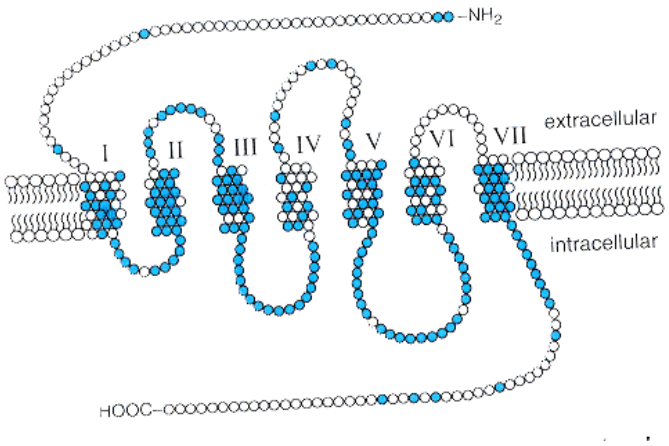
OPIATE/OPIOIDS PHARMACOLOGY

OPIATE/OPIOIDS PHARMACOLOGY

- Opiates work in the brain at specific “opiate receptors”
  - There are three types (Mu, Kappa e Delta) of opiate receptors but the main receptor is called “Mu”



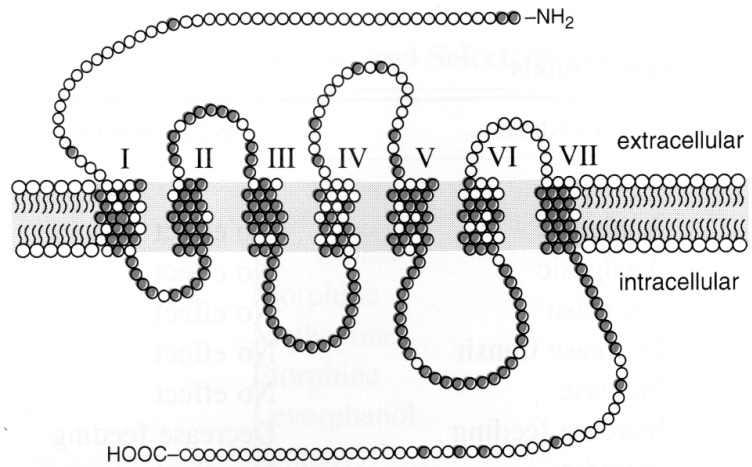
Schematic of Mu Opiate Receptor

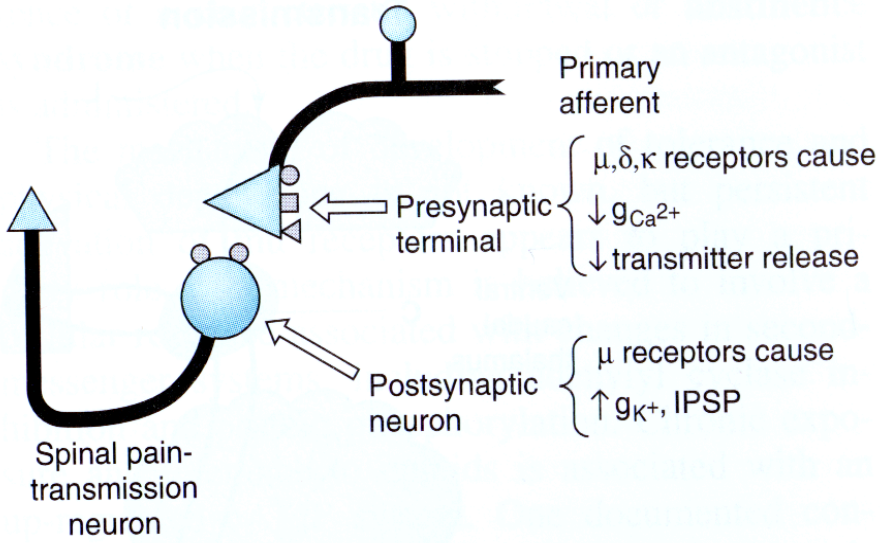
Source: Goodman and Gillman 9th ed, p. 526

In 1973, Candace Pert and Solomon H. Snyder published the first detailed binding study of what would turn out to be the Mu opioid receptor, using ^{3}H-naloxone

OPIOID RECEPTORS

Opioids bind to specific receptor molecule that mediates its effects. Several opioid specific receptors have been cloned: Mu, Kappa, and Delta receptors. These receptors belong to G protein-coupled seven transmembrane receptor family. The amino acid sequences are approximately 65% identical among these receptors, but they have little homology with other G protein-coupled receptors





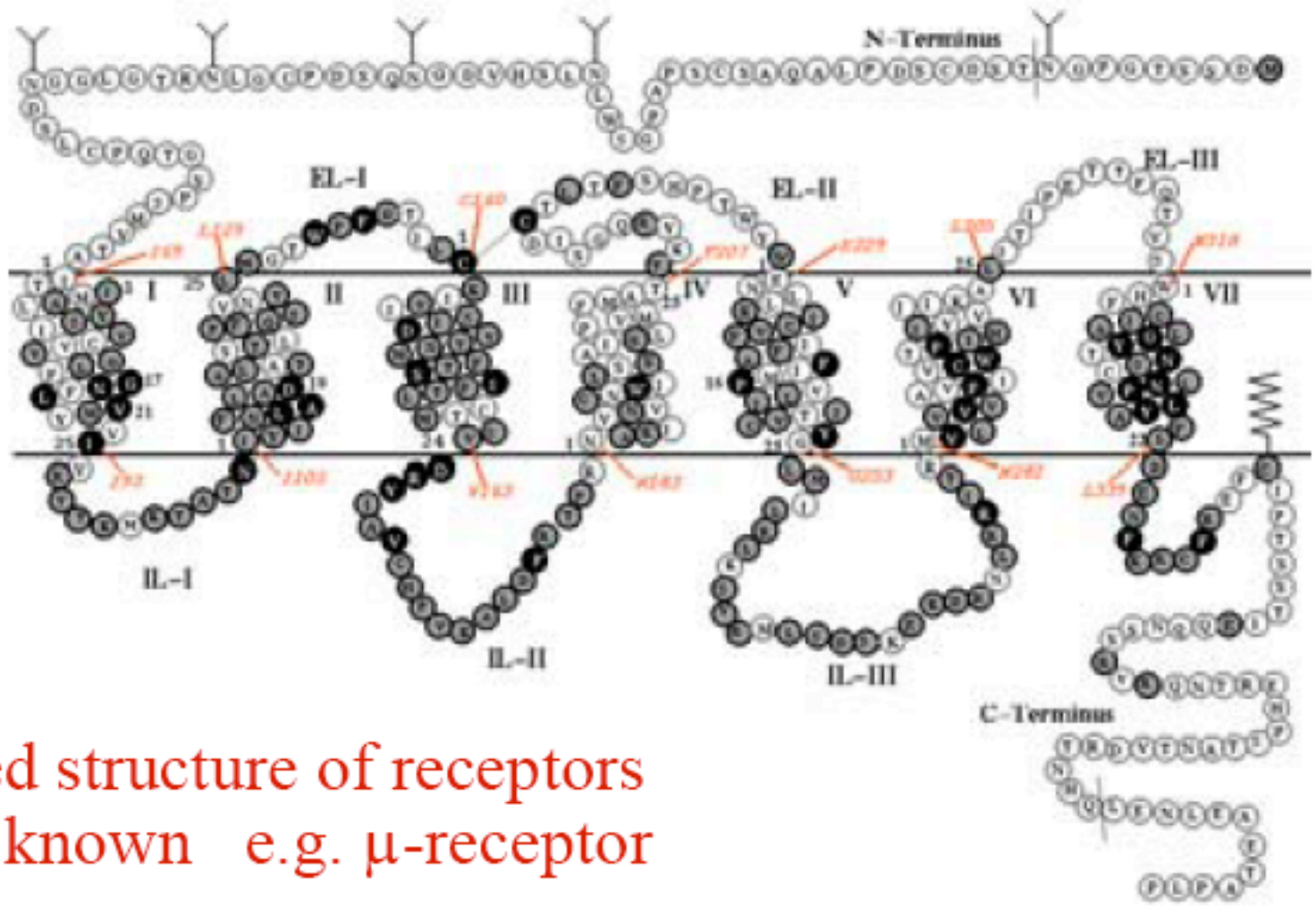
Mechanism of Opioid Receptor Function

1. Mu, Kappa, and Delta receptors are functionally coupled to pertussis toxin sensitive heterotrimeric G proteins (Gi) to inhibit adenylyl cyclase activity.

2. Activates receptor-activated K^+ currents which increase K^+ efflux (hyperpolarization) reduces voltage-gated Ca^{2+} entry.

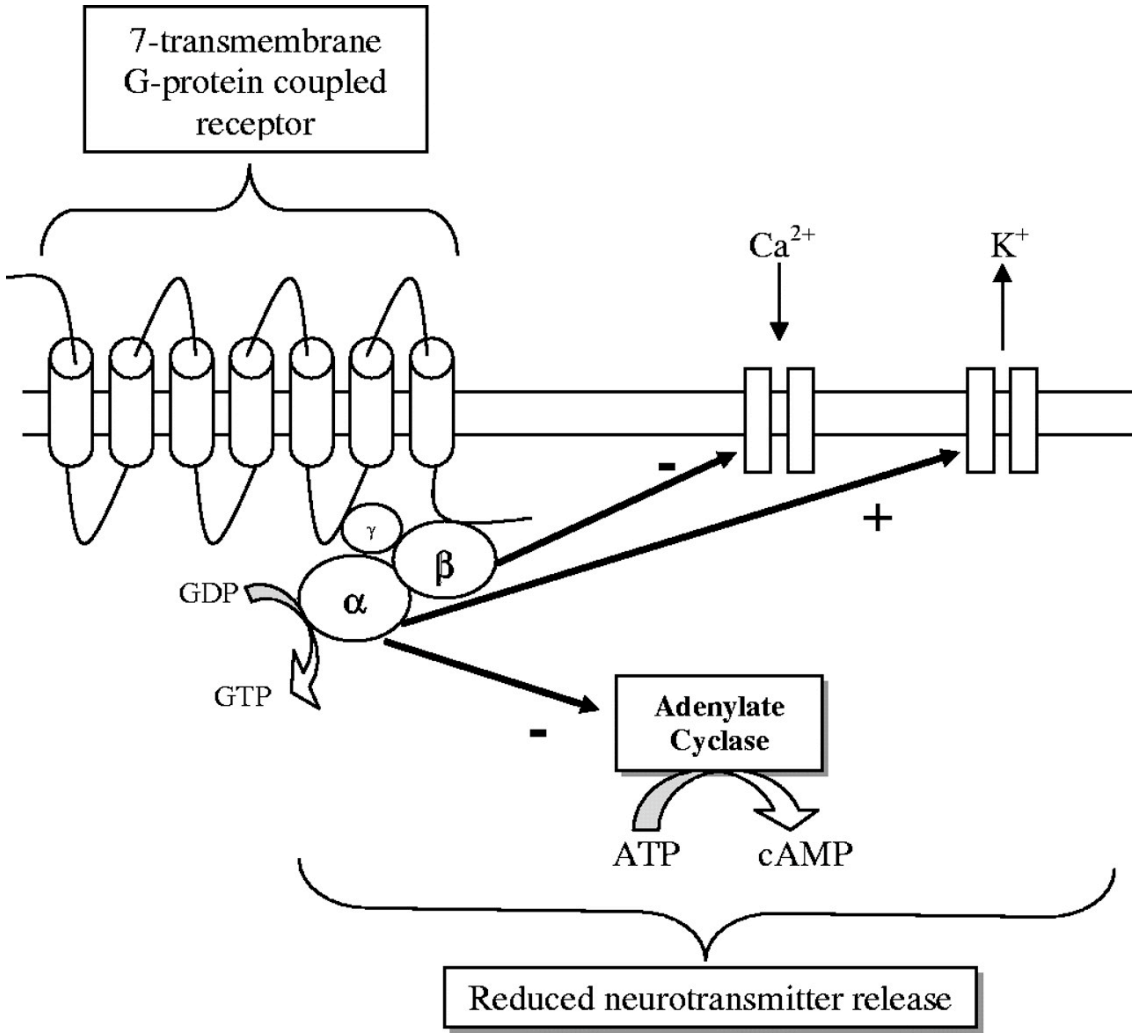
3. Hyperploarization of membrane potential by K^+ currents and inhibition of the Ca^{2+} influx prevents neurotransmitter release and pain transmission in varying neuronal pathways.

Receptor subtypes e.g. μ-receptor



Detailed structure of receptors
is now known e.g. μ-receptor

Seven transmembrane structure of opioid G-protein-coupled receptor.



Seven transmembrane structure of opioid G-protein-coupled receptor. Receptor activation by opioid receptor ligands leads to initiation of intracellular transduction pathways that include stimulation of potassium efflux, inhibition of VSCCs and inhibition of adenylyl cyclase. (McDonald J , Lambert D Contin Educ Anaesth Crit Care Pain 2005;5:22-25)

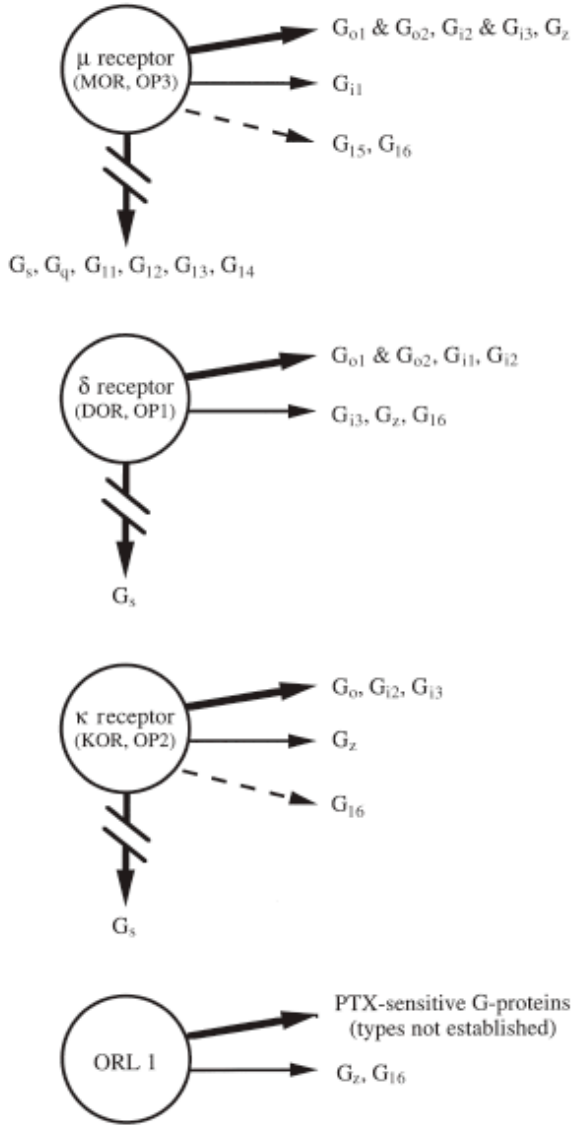


Fig. 1 A summary of the relative G-protein selectivity of each of the opioid receptors. The heavy arrow indicates those G-proteins preferentially stimulated by each receptor, including those for which there is some evidence for coupling in native tissue. The lighter arrow indicates that coupling between receptor and G-protein has been demonstrated but the functional significance of the coupling is less clear. The dashed arrow indicates that modest coupling has been demonstrated with recombinant G-protein and receptor. The broken arrow indicates those G-proteins to which the receptor does not couple.

OPIATE RECEPTORS AND ACTIVATION EFFECT

Although the ORL_1 receptor was accepted as a member of the "family" of opioid receptors on the basis of its structural homology towards the classical types, there is no corresponding pharmacological homology. Even non-selective ligands that exhibit uniformly high affinity towards m-, k- and d-receptors, have very low affinity for the ORL_1 receptor, and for this reason as much as for the initial absence of an endogenous ligand, the receptor was called an "orphan opioid receptor".

Nociceptin is the endogenous ligand for ORL_1 Nociceptin is an opioid-related peptide, is a potent anti-analgesic, widely distributed in the CNS, and may be involved in the phenomenon of opioid-induced hyperalgesia

OPIATE RECEPTORS AND ACTIVATION EFFECT

Mu_1 (μ_1) Located outside spinal cord	analgesia, euphoria
Mu_2 (μ_2) Located throughout CNS	constipation, respiratory depression
Kappa	spinal analgesia, dysphoria
Delta	analgesia thru the endorphin, enkephalin and dynorphin system

Tabella 31-1. Sottotipi recettoriali oppioidi, affinità per i peptidi oppioidi endogeni, e alcune delle loro funzioni

Sottotipo recettoriale	Funzioni	Affinità per i peptidi oppioidi endogeni
μ (mu)	Analgesia sopraspinale e spinale; sedazione; inibizione della respirazione; rallentato transito GI; modulazione del rilascio di ormoni e neurotrasmettitori	Endorfina > encefaline > dinorfine
δ delta)	Analgesia sopraspinale e spinale; modulazione del rilascio di ormoni e neurotrasmettitori	Encefaline >> endorfina e dinorfine
κ (kappa)	Analgesia sopraspinale e spinale; effetti psicotomimetici; rallentato transito GI	Dinorfine >> endorfina ed encefaline

GI, gastrointestinale.

Mu and Kappa Receptor Activation

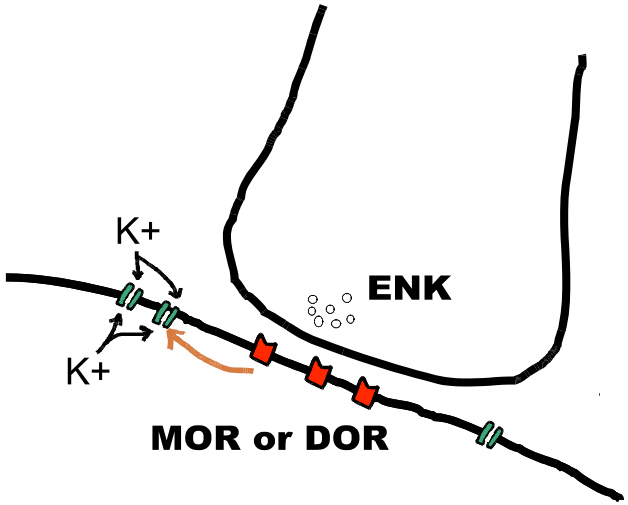
Response	Mu-1	Mu-2	Kappa
Analgesia	★	★	★
Respiratory Depression		★	
Euphoria		★	
Dysphoria			★
Decrease GI motility		★	
Physical Dependence		★	

Opioid Receptor Expression

Mu receptor	**periaqueductal gray, spinal trigeminal nucleus, cuneate and gracile nuclei, thalamus regions, dorsal horn of the spinal cord (DHSC)**	**μ_1: analgesia physical dependence** **μ_2:** **respiratory depression** **miosis** **euphoria** **reduced GI motility** **physical dependence** **μ_3:** **unknown**
	nucleus of solitract, nucleus ambiguus	
	parabrachial nucleus	
k receptor	**neurons of the postrema**	**analgesia** **sedation** **miosis**
	hyphothalamic region, DHSC	**inhibition of ADH release** **dysphoria**
Delta receptor	**DHSC**	**analgesia** **antidepressant effects** **physical dependence**

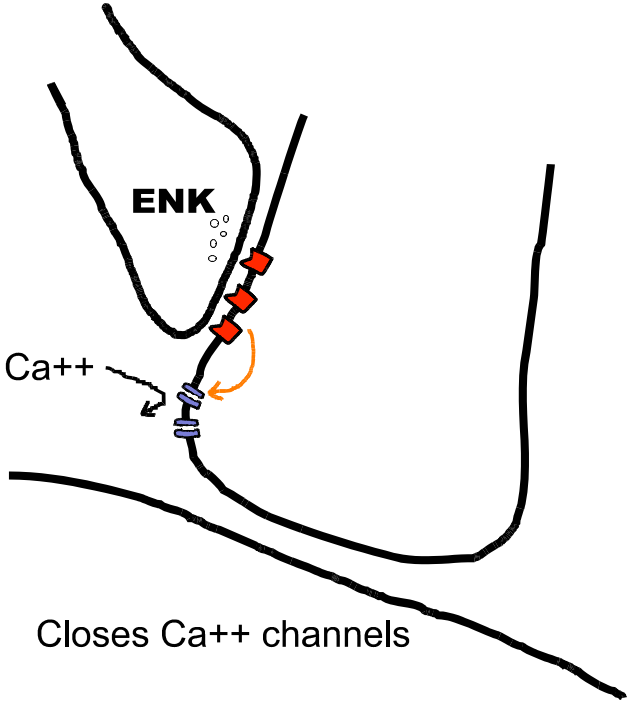
Endogenous opiates can cause post or pre synaptic inhibition

Post synaptic inhibition



Opens K+ channels

Pre synaptic inhibition



Closes Ca++ channels

Endogenous opioids

Enkephalins

Endorphins

Dynorphins

Endomorphins

Plus Nociceptin – mixed analgesic and hyperalgesic actions…

The opioid peptides precursors

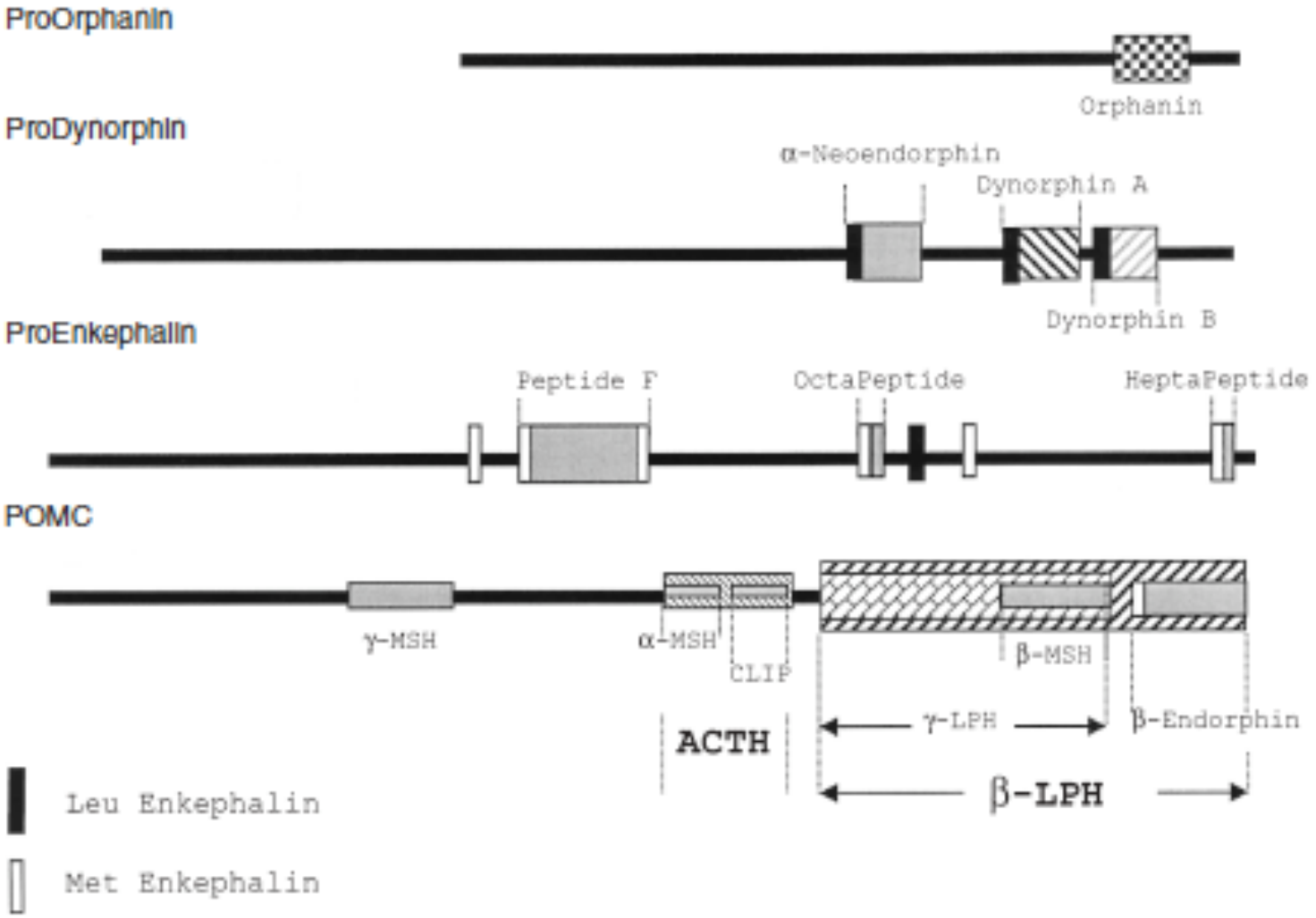


FIGURE 3.1. The opioid-peptide precursors. (From Akil H, Owens C, Gutstein H, et al. Endogenous opioids: overview and current issues. *Drug Alcohol Depend* 1998;51:127–140, with permission.)

Endogenous Opioids:
Enkepalins , Endorphins, Dynorphins, Endomorphins

Enkepalins:
Met-Enkepalin **Tyr-Gly-Gly-Phe**-Met
Leu- Enkepalin **Tyr-Gly-Gly-Phe**-Leu

Endorphins:
alpha-neoendorphin **Tyr-Gly-Gly-Phe**-Leu-Arg-Lys-Tyr-Pro-Lys
beta-neoendorphin **Tyr-Gly-Gly-Phe**-Leu-Arg-Lys-Tyr-Pro
beta-endorphin **Tyr-Gly-Gly-Phe**-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-
Thr-leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu (31-Residues)

Dynorphins:
Dynorphin A **Tyr-Gly-Gly-Phe**-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Dynorphin B **Tyr-Gly-Gly-Phe**-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr

Endomorphins:
Endomorphin 1 Tyr-Pro-Trp-Phe-NH2
Endomorphin 2 Tyr-Pro-Phe- Phe-NH2

.

Endogenous opioids.

Enkephalins.

- **Small peptides, 5 amino acids**
- **2 versions, leucine enkephalin, methionine enkephalin, differ by one amino acid.**
- **Synthesised in parallel, similar actions.**
- **Inhibitory neurotransmitters, mostly small interneurones, in PAG, RVM (rostral ventromedial medulla), dorsal horn plus several other sites.**

Endogenous opioids.

***Endorphins*.**

- **Mostly beta-endorphin.**
- **31 amino acid peptide, includes met-enkephalin sequence, but synthesised separately**
- **Synthesised from precursor that also creates melanocyte stimulating hormone and corticotrophin (adrenal cortex-stimulating hormone).**
- **Found in pituitary and hypothalamus.**
- **Beta endorphin containing nerve fibres spread widely from neurones in the hypothalamus, to make inhibitory contacts with target neurones in regions including the PAG, but not significantly the rostral ventromedial medulla (RVM)**

Endogenous opioids.

***Dynorphins*.**

- **Several forms, 10-17 amino acids.**
- **Include Leu-enkephalin sequence in structure, but synthesised independently.**

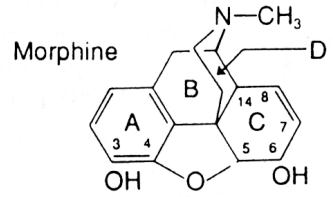
***Endomorphins*.**

- **2 forms, both just 4 amino acids.**
- **No homology to other opioids.**
- **Recently discovered, importance yet to be established.**

SELECTIVITY OF OPIOID DRUGS AND PEPTIDES FOR DIFFERENT RECEPTORS

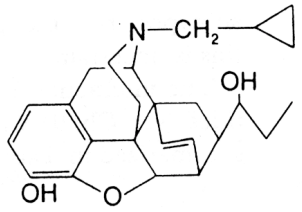
Compund	Mu	K	Delta
Endogenous Peptides			
Met-enkephalin	++	+++	
Leu-enkephalin	++	+++	
beta-Endorphi	+++	+++	
alfa-Neoendorphin	+	+	+++
Dynorphin A	++		+++

Morphine and its analogues



Drug	Substituents			
	3	6	N	14
Morphine	—OH	—OH	—CH_3	—H
Heroin	—OCO · CH_3	—OCO · CH_3	—CH_3	—H
Codeine	—OCH_3	—OH	—CH_3	—H
Levorphanol	—OH	—H	—CH_3	—H (lacks —O— at C_4–C_5)
Dihydrocodeine	—OCH_3	—OH	—CH_3	—H (lacks double bond C_7–C_8)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—H
Nalbuphine	—OH	—OH	—CH_2—cyclobutyl	—OH (lacks double bond C_7–C_8)
Butorphanol	—OH	—H	—CH_2—cyclobutyl	—H (lacks —O— at C_4–C_5 & double bond C_7–C_8)
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	—HO (lacks double bond C_7–C_8)

Buprenorphine



3. Opioid Analgesic Drugs

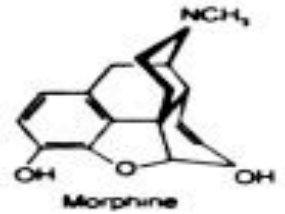
The drugs used to alleviate moderate to severe pain are either opiates (derived from the opium poppy) or opiate-like (synthetic drugs). These drugs are together as **OPIOIDS.**

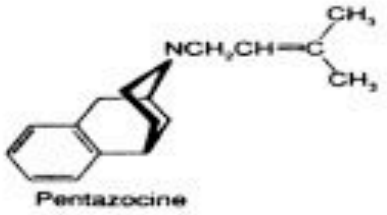
Examples: Opiates: morphine, codeine

Opiate-Like: fentanyl, meperidine, methadone

See below the structures of some opioid analgesic drugs and derivatives

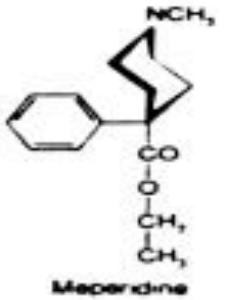
Morphine

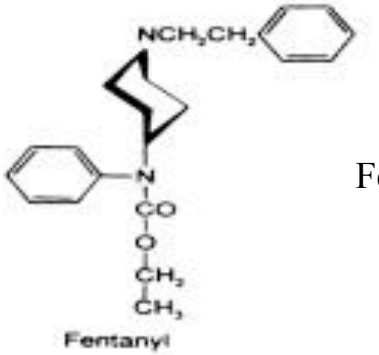




Pentazocine

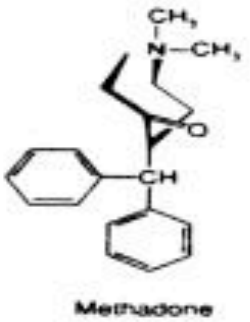
Meperidine

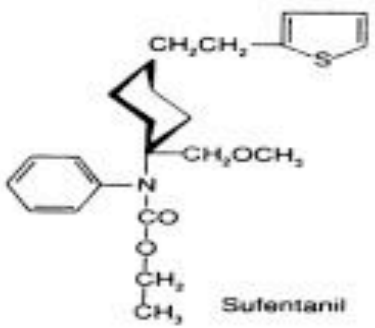




Fentanyl

Methadone





Sufentanil

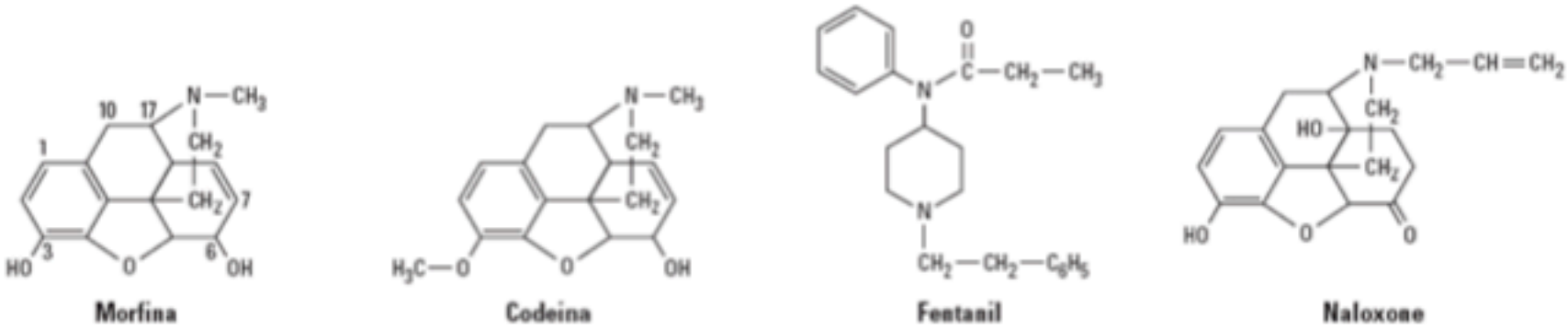
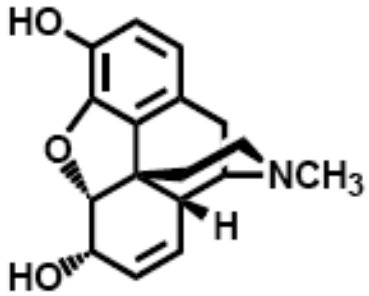


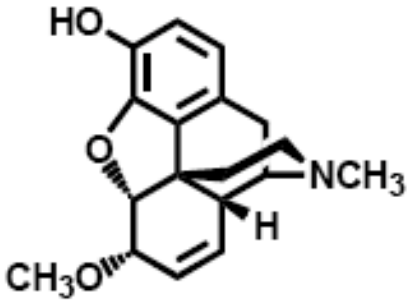
Figura 31-1. Strutture chimiche di tre analgesici e antagonisti oppioidi.

Dal Volume: Farmacologia generale e clinica

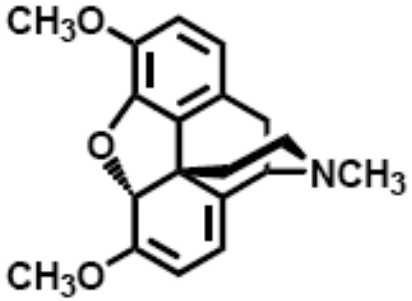
Natural products



Morphine 10-16%



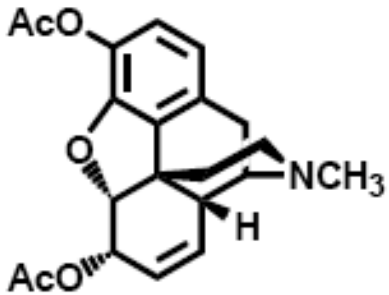
Codeine 0.8-2.5%

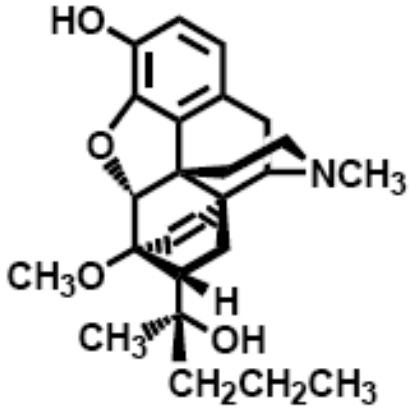


Thebaine 0.8-2%

Semisynthetic opioids

Heroin





Etorphine

RECEPTOR BINDING AT MU RECEPTOR

Agonist	**Morphine-like effect (e.g. heroin and methadone weak binding except for Fentanyl)**
Partial Agonist	**Weak morphine-like effects with strong receptor affinity (e.g. buprenorphine)**
Antagonists	**No effect in absence of an opiate or opiate dependence (e.g. naloxone and naltrexone)**

Partial vs Full Opiate Mu Agonist

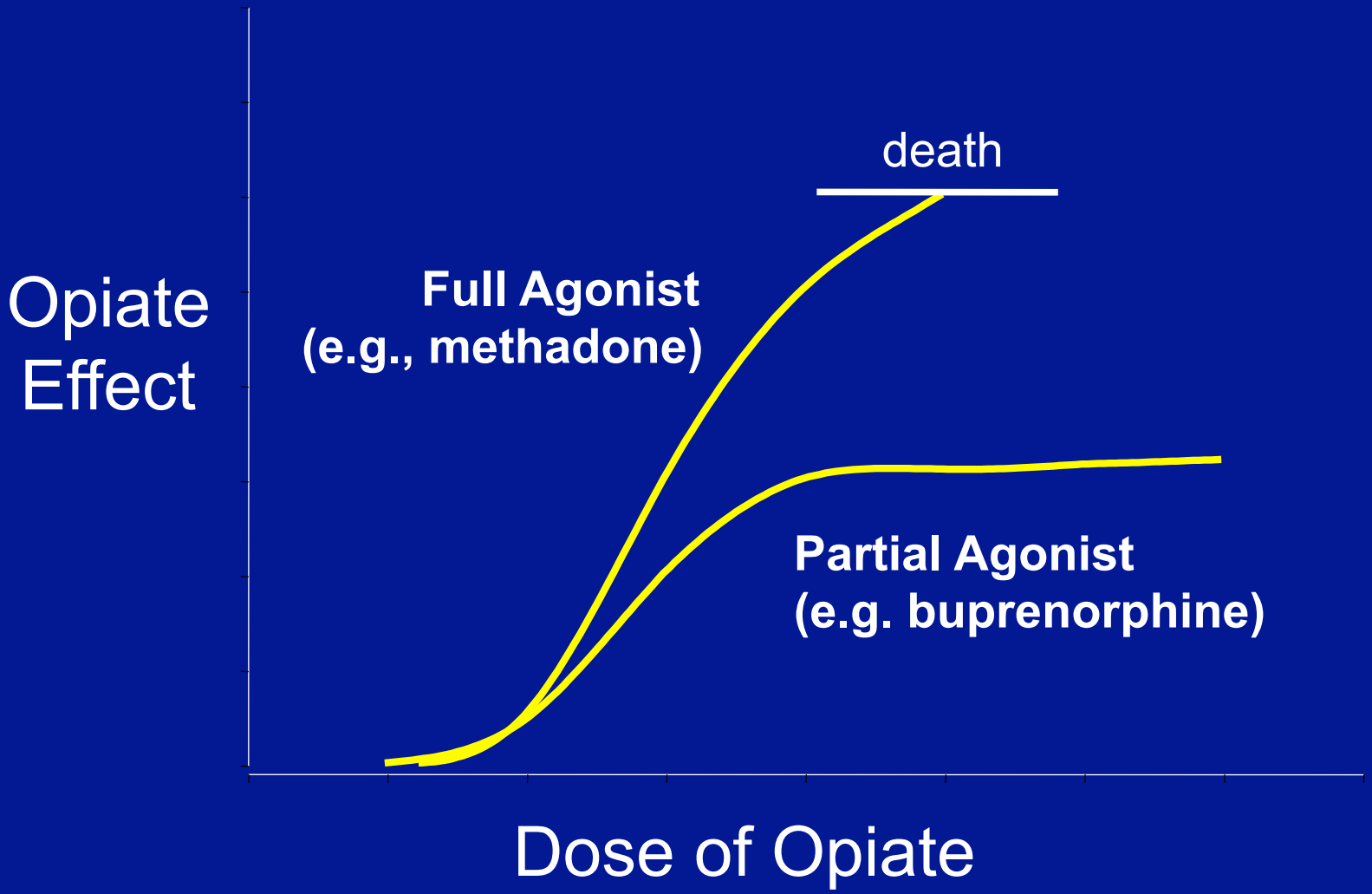


Table 1. *Analgesic effects at opioid receptors.*

	Mu (μ)	**Delta (δ)**	**Kappa (κ)**
	• Mu 1 – Analgesia • Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	• Analgesia, spinal analgesia	• Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea
Endogenous Peptides			
Enkephalins	Agonist	Agonist	
β-Endorphin	Agonist	Agonist	
Dynorphin A	Agonist		Agonist
Agonists			
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl	Agonist		
Meperidine	Agonist	Agonist	
Methadone	Agonist		
Antagonists			
Naloxone	Antagonist	Weak Antagonist	Antagonist
Naltrexone	Antagonist	Weak Antagonist	Antagonist

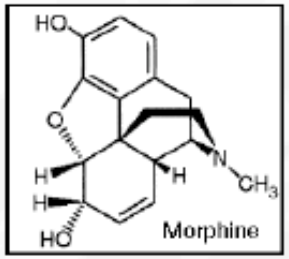
Modified from Miller's Anesthesia (4)

Tabella 31-2. Analgesici oppioidi comuni

Nome generico	Dose (mg)	Rapporto potenza orale/ parenterale	Durata della analgesia (ore)	Attività intrinseca
Morfina[1]	10	Basso	4-5	Elevata
Idromorfone	1,5	Basso	4-5	Elevata
Oximorfone	1,5	Basso	3-4	Elevata
Metadone	10	Alto	4-6	Elevata
Petidina	60-100	Medio	2-4	Elevata
Fentanil	Da titolare	Solo uso parenterale	0,25-075	Elevata
Sufentanil	0,02	Solo uso parenterale	1-1,5	Elevata
Alfentanil	Da titolare	Solo uso parenterale	0,25-0,75	Elevata
Levorfanolo	2-3	Alto	4-5	Elevata
Codeina	30-60[4]	Alto	3-4	Bassa
Idrocodone[2]	5-10	Medio	4-6	Moderata
Oxicodone[1,3]	4,5[4]	Medio	3-4	Moderata
Propoxifene	60-120[3,4]	Solo uso orale	4-5	Molto bassa
Pentazocina	30-50[4]	Medio	3-4	Moderata
Nalbufina	10	Solo uso parenterale	3-6	Elevata
Buprenorfina	0,3	basso	4-8	Elevata
Butorfanolo	2	Solo uso parenterale	3-4	Elevata

[1] Disponibile in forme a rilascio sostenuto, Morfina (MSContin); oxicodone (OxyContin).
[2] Disponibile in preparazioni contenenti paracetamolo.
[3] Disponibile in preparazioni contenenti paracetamolo, aspirina.
[4] Efficacia analgesica a questa dose non equivalente a 10 mg di morfina (v. testo).

Opioid Analgesics

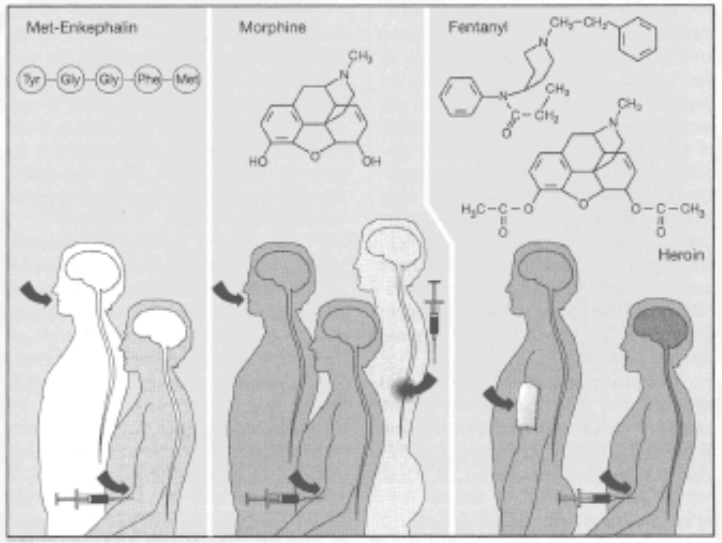


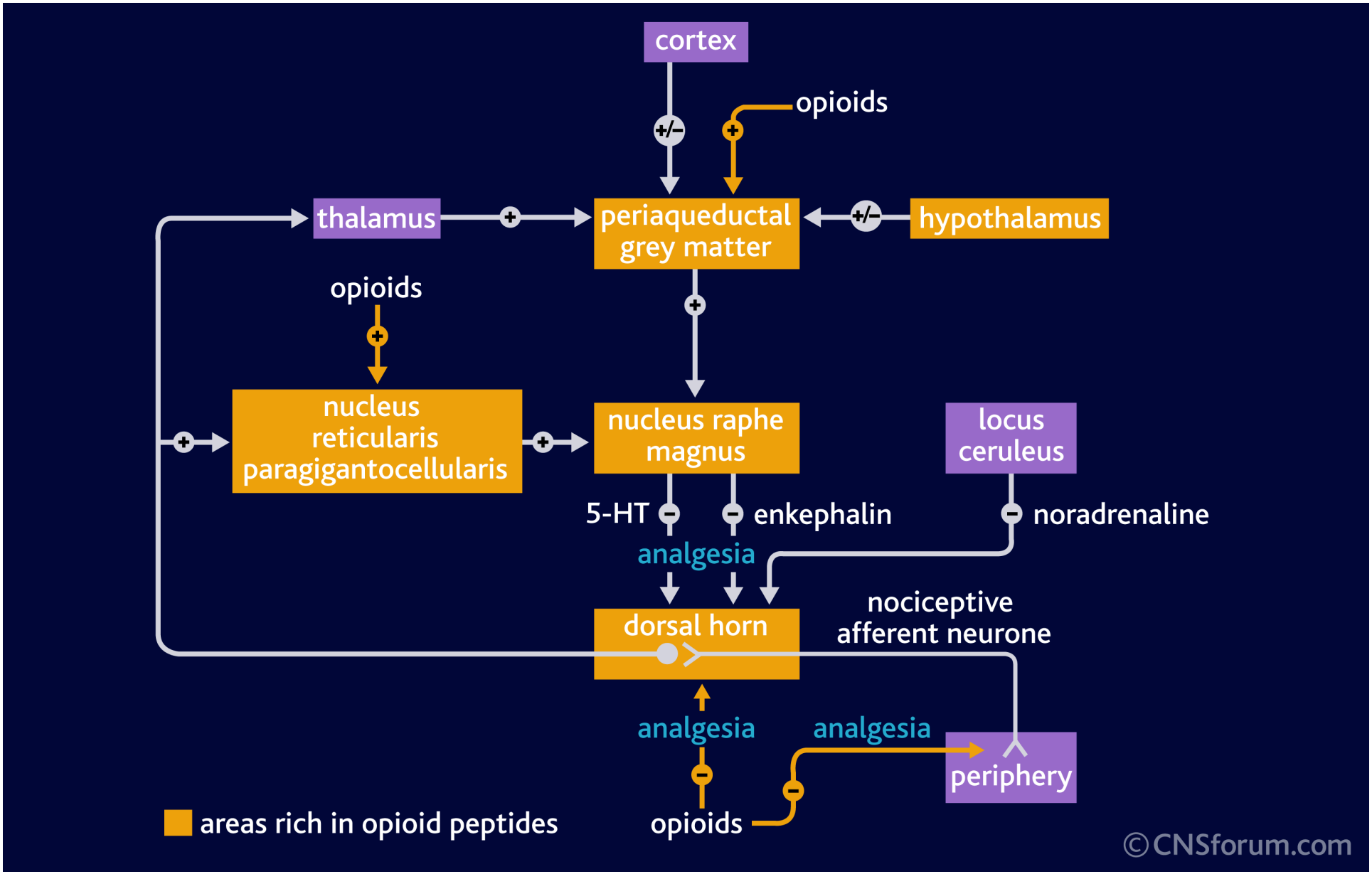
Opiates:

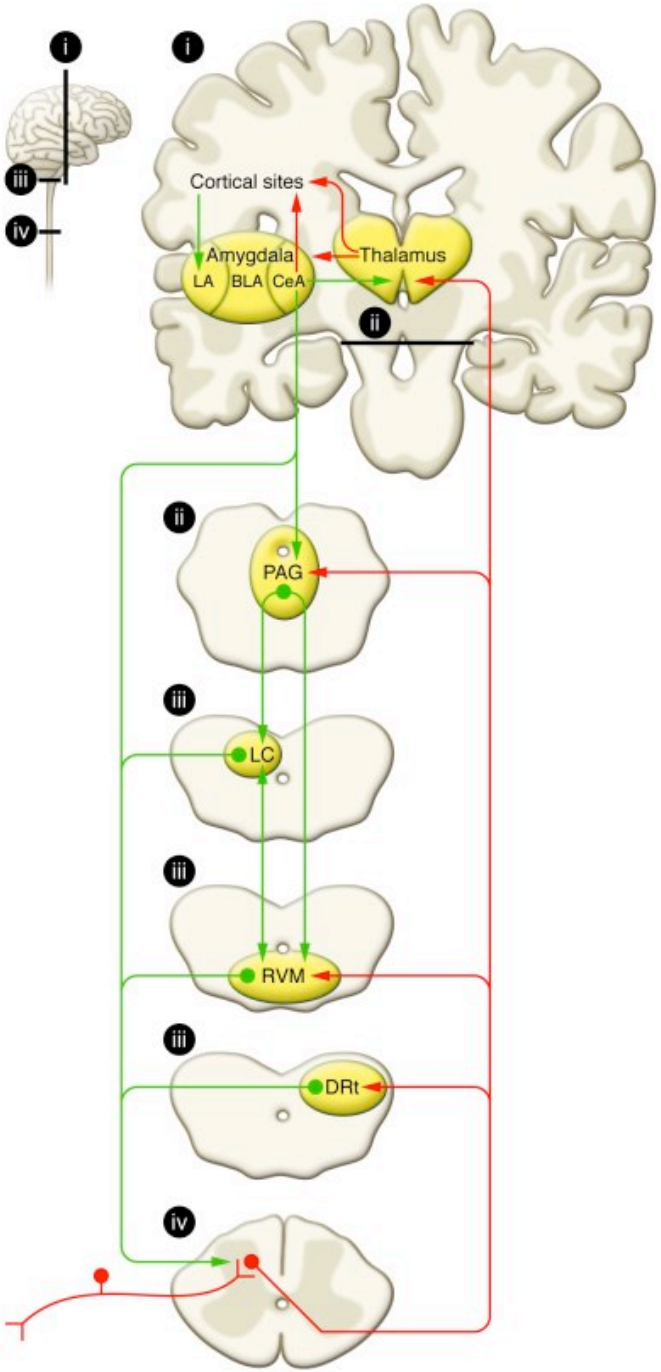
Mechanism of analgesic action:

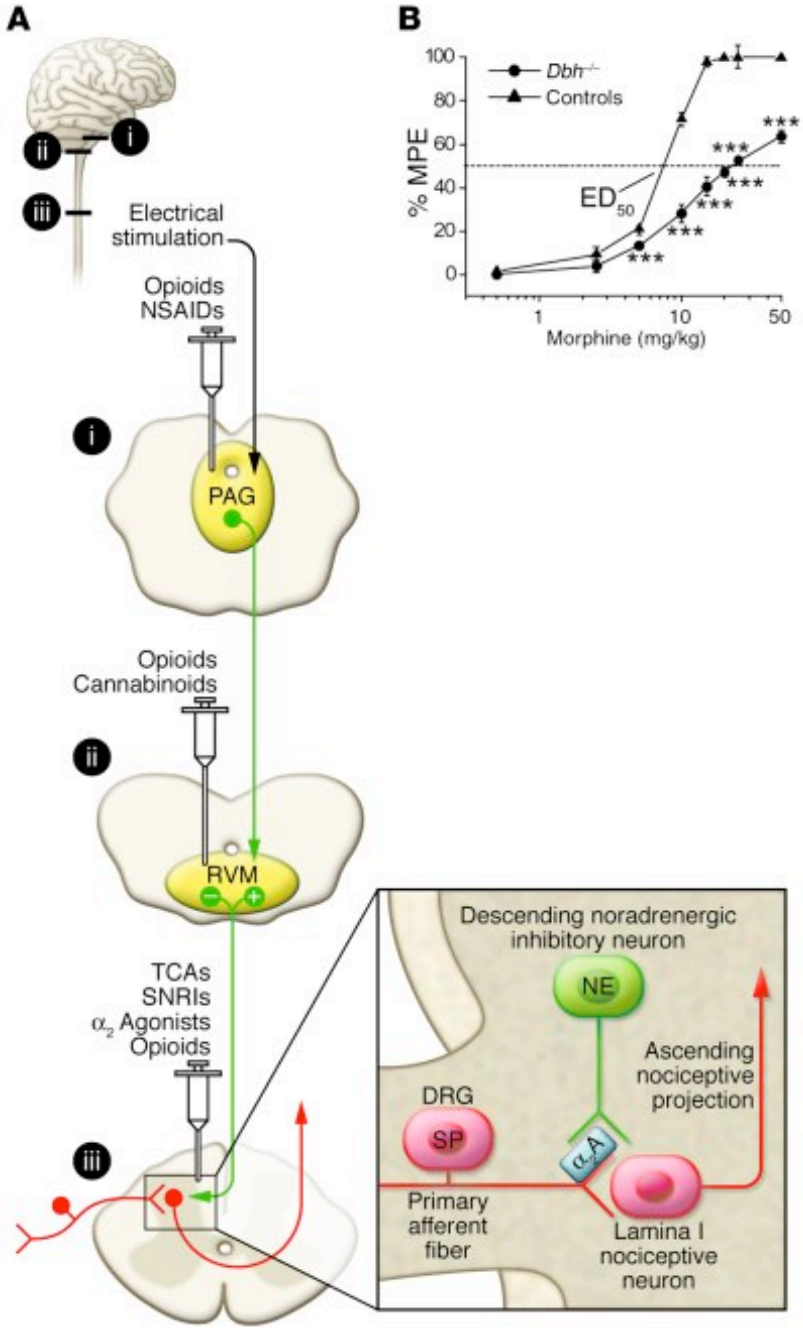
- Spinal analgesia:
  Activation of presynaptic opioid receptors => decreased Ca^{++} flux => decreased neurotransmitter (Substance P) release => decreased transmission of pain signal from nocireceptors
- Supraspinal analgesia:
  Activation of postsynaptic opioid receptors in the medulla and midbrain => increased K^{+} flux => hyperpolarization => inhibition of neurons in the pain pathway

- Oral opioids are subject to first-pass elimination => low oral bioavailability
- Morphine is metabolized and eliminated via glucuronidation
- Heroin, Fentanyl: very lipophilic => rapid accumulation in the CNS




cortex
opioids
+/−
+
thalamus
periaqueductal grey matter
+/−
hypothalamus
opioids
+
+
+
nucleus reticularis paragigantocellularis
nucleus raphe magnus
locus ceruleus
5-HT
enkephalin
noradrenaline
analgesia
dorsal horn
nociceptive afferent neurone
analgesia
analgesia
periphery
areas rich in opioid peptides
opioids
©CNSforum.com


i
i
iii
iv
Cortical sites
Amygdala
LA BLA CeA
Thalamus
ii
ii
PAG
iii
LC
iii
RVM
iii
DRt
iv


A
B
i
ii
iii
Electrical stimulation
Opioids NSAIDs
PAG
Opioids Cannabinoids
RVM
TCAs SNRIs
α_2 Agonists Opioids
Descending noradrenergic inhibitory neuron
NE
Ascending nociceptive projection
DRG
SP
α_2A
Primary afferent fiber
Lamina I nociceptive neuron
100
80
60
40
20
0
% MPE
Dbh−/−
Controls
ED50
***
1
10
50
Morphine (mg/kg)

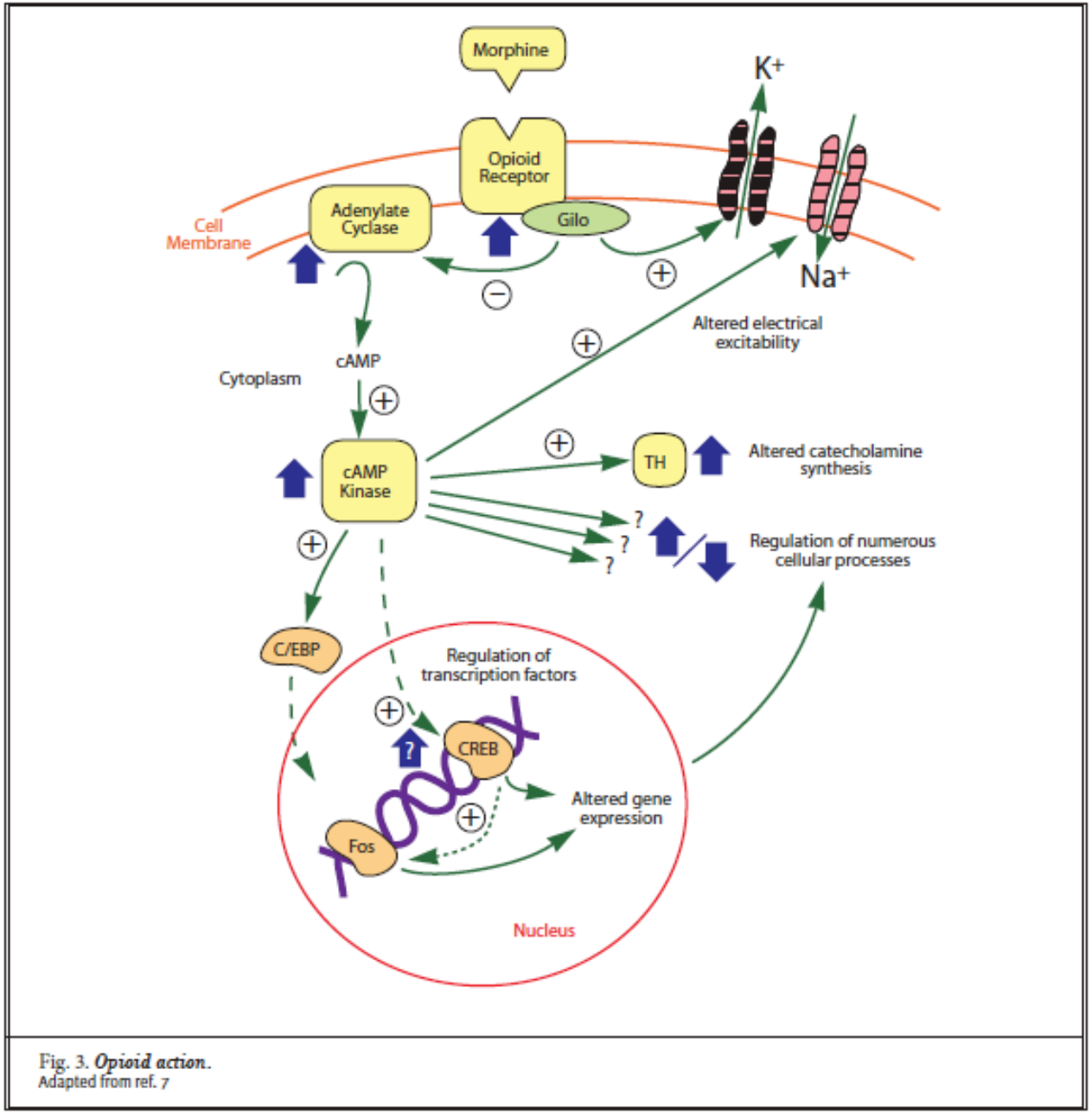
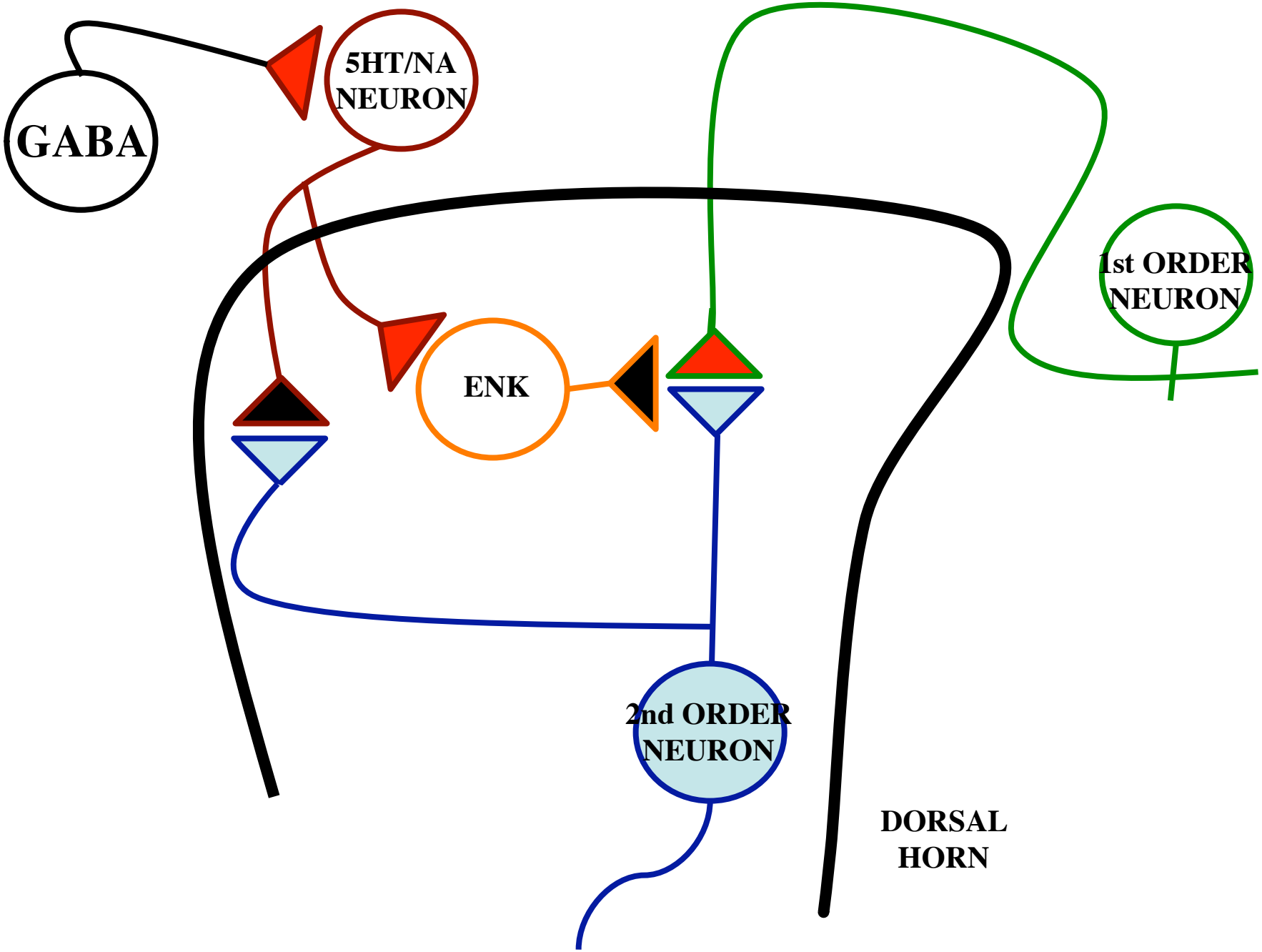
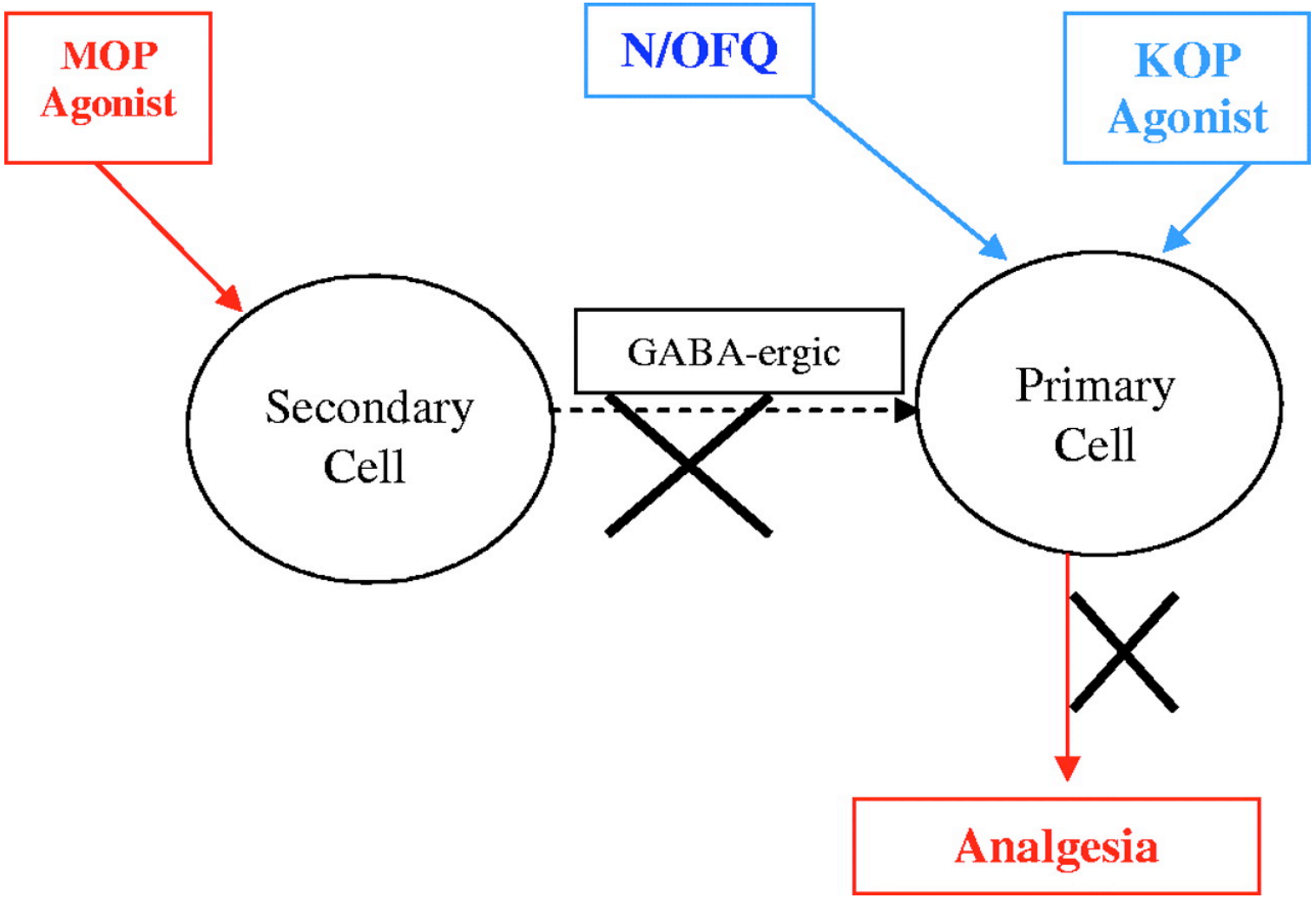


Fig. 3. *Opioid action.*
Adapted from ref. 7

SUPRASPINAL ANALGESIA



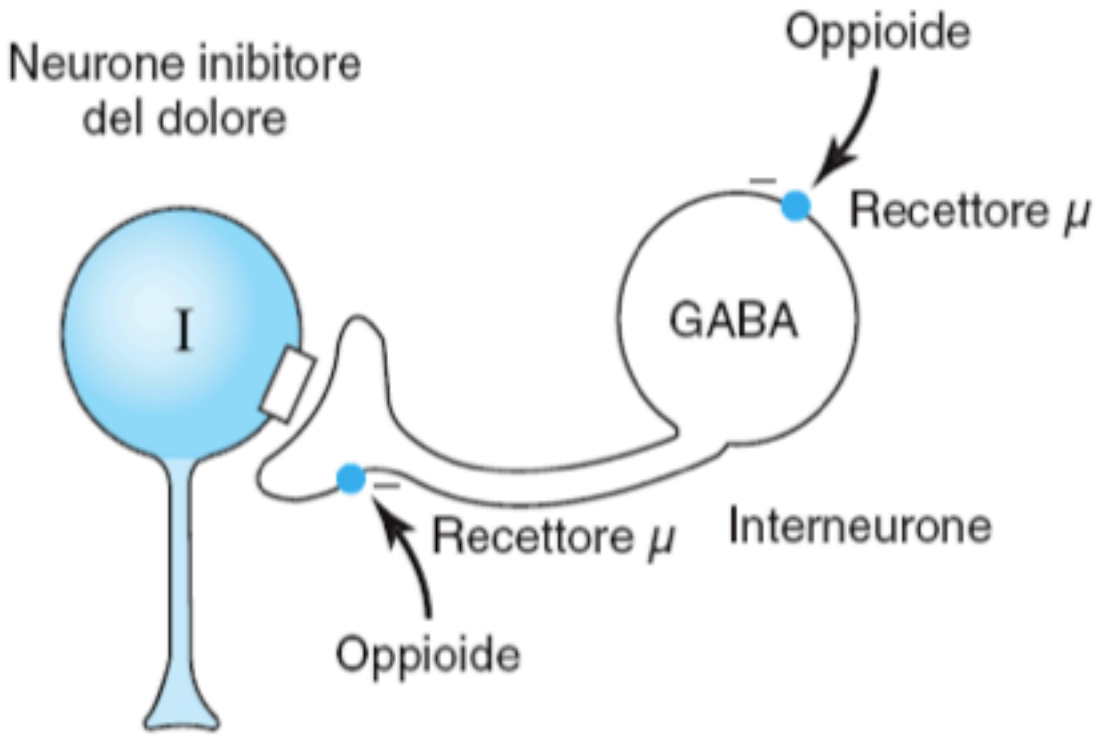
In the NRM stimulation of primary cells is thought to induce analgesia via activation of descending inhibitory control pathways and release of endogenous opioids.



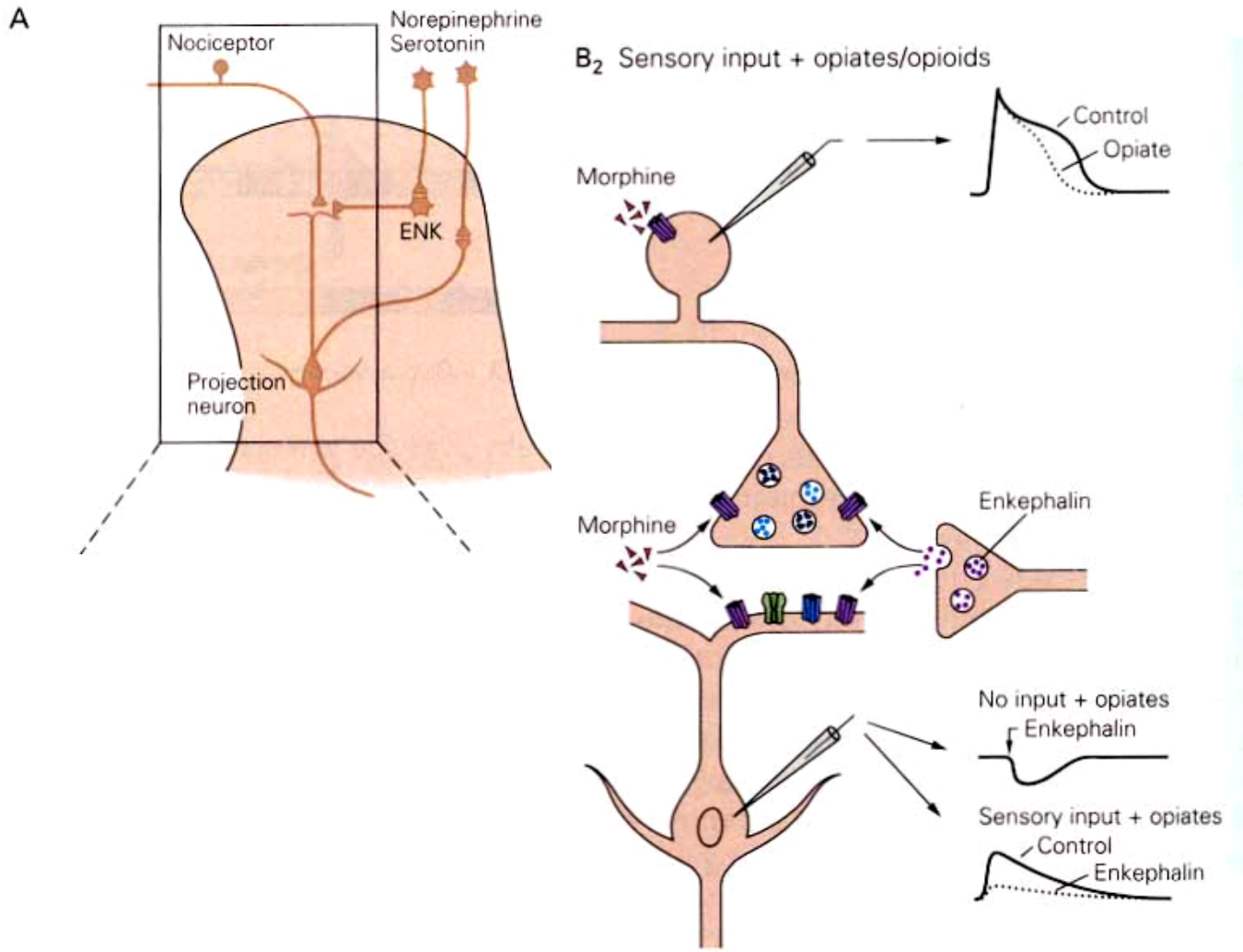
McDonald J , Lambert D Contin Educ Anaesth Crit Care Pain 2005;5:22-25

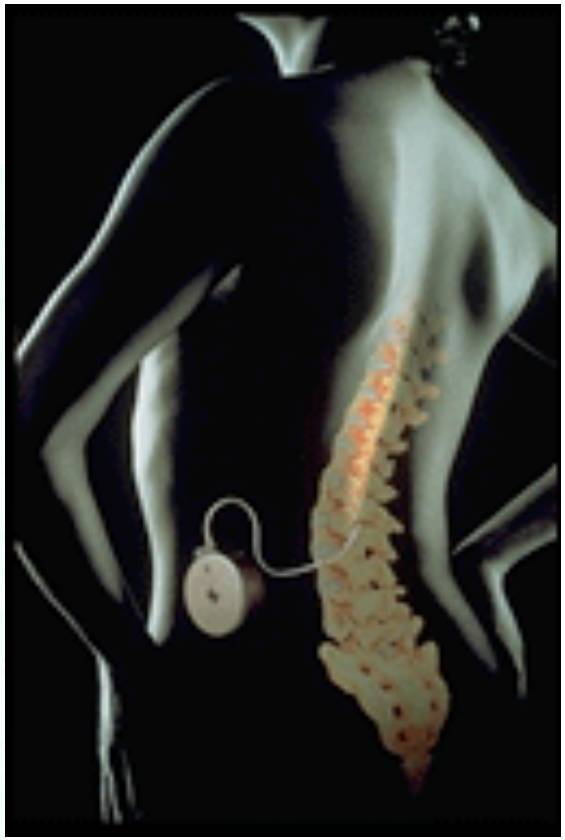
Continuing Education in Anaesthesia, Critical Care & Pain

Figura 31-4. Circuiti locali dell'asse cerebrale che sottendono all'analgesia oppioide mediata dai recettori μ. Il neurone inibitore del dolore (I) è eccitato indirettamente dagli oppioidi (esogeni o endogeni) che inibiscono un interneurone inibitorio GABAergico (GABA).



SPINAL ANALGESIA





INHIBITION OF NEUROTRANSMITTERS RELEASE

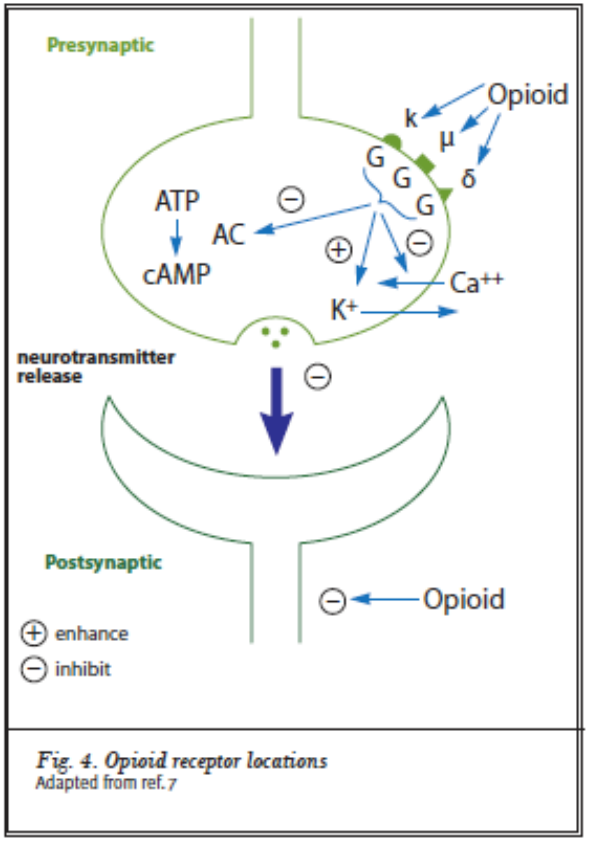


Fig. 4. Opioid receptor locations
Adapted from ref. 7

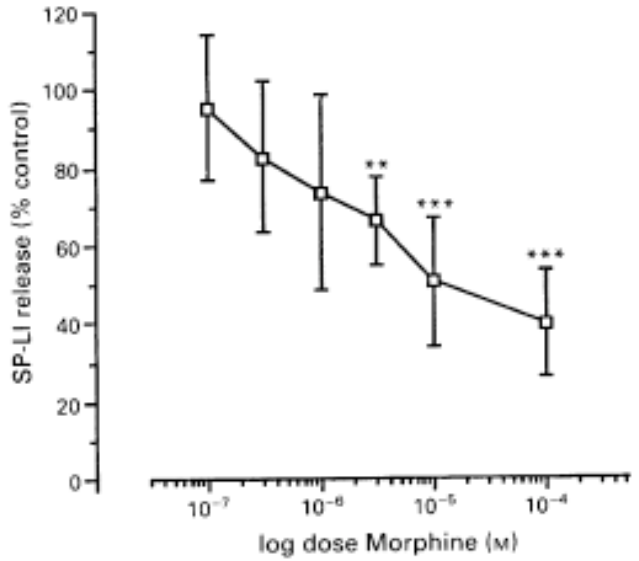


Figure 1 Effect of morphine on substance P-like immunoreactivity (SP-LI) release evoked by KCl 60 mM. Data are mean differences for 10 animals; vertical bars show s.e.mean. *** $P < 0.001$; ** $P < 0.01$.

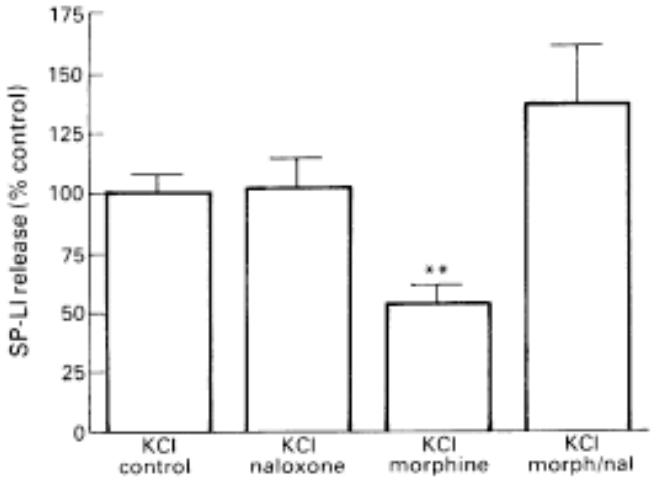
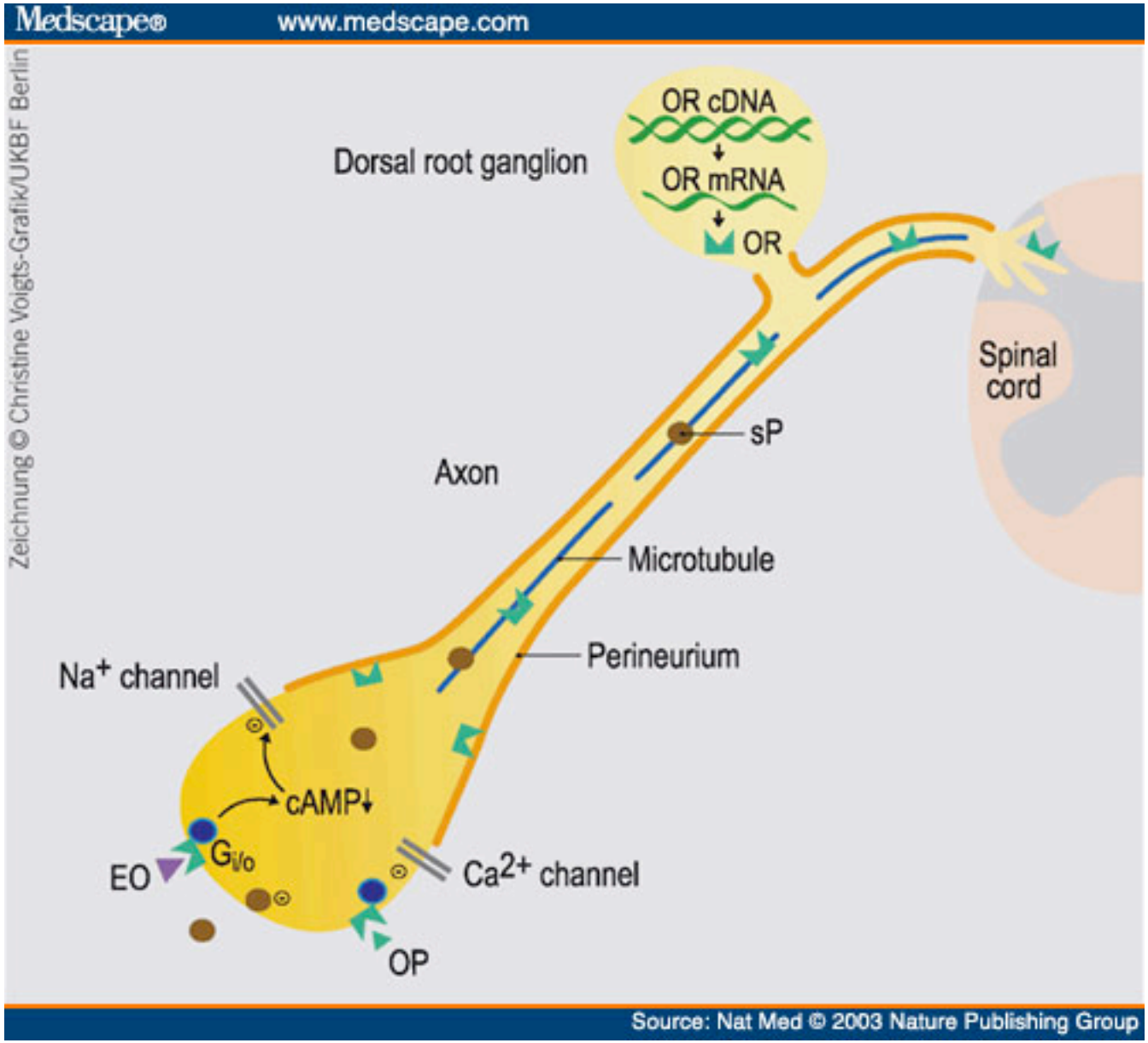


Figure 2 Effect of naloxone (100 nM) on morphine (30 μM)-sensitive substance P-like immunoreactivity (SP-LI) release evoked by KCl 60 mM. Data are means expressed as a percentage of 60 mM KCl-stimulated control; vertical bars show s.e.mean. ** $P < 0.01$ compared to control. $n = 9$ for control; $n = 7$ for naloxone; $n = 8$ for morphine; $n = 6$ for morphine (morph) plus naloxone (nal).

Primary Effect of Opioid Receptor Activation

- Reduction or inhibition of neurotransmission, due largely to opioid-induced presynaptic inhibition of neurotransmitter release
- Involves changes in transmembrane ion conductance
  - Increase potassium conductance (hyperpolarization)
  - Inactivation of calcium channels

Opioid receptor transport and signaling in primary afferent neurons



Opioid receptors are synthesized in the dorsal root ganglion and transported along intra-axonal microtubules into central and peripheral processes of the primary afferent neuron. At the terminals, they become functional receptors.
Upon activation by exogenous or endogenous opioids, they couple to inhibitory G-proteins. This leads to direct or indirect (through decrease of cyclic adenosine monophosphate) suppression (-) of Ca^{2+} or Na^{+} currents, and subsequent attenuation of substance P release.

OR, opioid receptor; sP, substance P; EO, exogenous opioids; OP, endogenous opioid peptides; $G_{i/o}$, inhibitory G proteins; cAMP, cyclic adenosine monophosphate.

Pharmacological actions of the opioids

- analgesia
- respiratory depression (→ death)
- euphoria → μ receptors
  κ receptors → dysphoria
- sedation
- constipation
- cough suppression (antitussive)
- nausea, vomiting
- (tolerance, dependence)


BAYER
PHARMACEUTICAL PRODUCTS.
ASPIRIN
HEROIN
HEROIN HYDROCHLORIDE
FARBENFABRIKEN OF ELBERFELD CO.
40 Stone Street, New York.

1897 Bayer advertisement
ASPIRIN
The Substitute for Salicylates
HEROIN
The Sedative for Coughs

PHARMACOLOGIC ACTIONS

Morphine and related opioids produce their major effects on the central nervous system and gastrointestinal tract

A. Central Nervous System

1. Analgesia

produces selective attenuation of pain perception; effect is dose-dependent

therapeutic dose (10 mg; parentral)

pain less intense (pain threshold not elevated)
less discomfort (more effective for dull pain)
euphoria
drowsiness

higher doses (15 – 20 mg; parentral)

pain threshold elevated
respiratory depression may be significant
sharp intermittent pain relieved
these doses DO NOT produce slurred speech, motor ataxia or protection from seizures

Sites of action

Periaqueductal Grey (PAG)
Caudal brain stem (nucleus raphe magus, magnocellular reticular formation)
Spinal cord
Limbic system

Mechanism of action

opioids generally produce inhibition of neuronal activity
opioids inhibit the release of neurotransmitters
opioids activate descending inhibitory systems

2. SEDATION: In humans, opioids usually produce sedation; however, in extremely high doses opioids produce convulsions (e.g., meperidine)

3. EUPHORIA: Euphoria is often produced by opioids. Euphoria is more prominent in those previously addicted to opioids

5. RESPIRATORY DEPRESSION:

Produced even in small doses
Large doses may induce respiratory failure
Death from morphine overdose is usually due to respiratory failure
Pain can stimulate respiration
Opioids decrease sensitivity of brain stem centers to CO2 (i.e., depress CO2 sensing capacity)
Pure oxygen can induce apnea during severe respiratory depression

6. NAUSEA AND VOMITING:

Opioids can stimulate the chemoreceptor trigger zone (CTZ)
Located in the area postrema in the medulla oblongata

Symptoms can be controlled by Phenothiazines

7. COUGH REFLEX (antitussive effect):

Opioids suppress the cough reflex
Produced by depression of neurons in medulla which control the cough reflex
Codeine is a potent inhibitor of the cough reflex
Dextromethorphan has no GI effects, no respiration depression, no analgesia

8. PUPILLARY DIAMETER:

Opioids cause miosis (pupillary constriction). Opioids act stimulate oculomotor nucleus to constrict pupil.
Pin point pupils are characteristics of morphine overdose. There is very little tolerance to this effect.

B. GASTROINTESTINAL TRACT

Decreases GI motility
Increases GI tone
Produces constipation (Diphenoxylate-meperidine derivative [Lomotil])
GI spasms can be controlled by atropine (acetyl choline receptor antagonist)
Biliary tract spasm. Opioids can exacerbate biliary colic

C. CARIOVASCULAR SYSTEM

No prominent effects
Peripheral vasodilation most prominent effect due to histamine release and decreased adrenergic tone
Very high doses may produce bradycardia
Orthostatic hypotension

D. URINARY TRACT

Opioids produce urinary retension
Increase tone of urinary sphincter
Decrease urine production (increased ADH secretion)

E. UTERUS

Duration of labor may be prolonged

F. BRONCHIAL SMOOTH MUSCLE

Therapeutic doses have no effect
High doses produce constriction (can aggravate asthma)

Pharmacological effects cont'd.

- Nausea and vomiting
  - Stimulation of receptors in an area of the medulla called the chemoreceptor trigger zone causes nausea and vomiting
  - Unpleasant side effect, but not life threatening

  - Other effects
  - Opioids can release histamines causing itching or more severe allergic reactions including bronchoconstriction

PHARMACOKINETICS

i. Absorption:

Readily absorbed from all sites of administration

ii. Distribution:

Distributed to all tissues

Morphine is poorly transported across the blood-brain barrier

iii. Metabolism:

The major mechanism is conjugated with glucuronic acid in the liver. **Morphine** is subject to significant “first-pass” metabolism in the liver.

iv. Excretion:

Free and conjugated morphine are excreted in the urine

THERAPEUTIC INDICATIONS

PAIN

i. Chronic pain (only under some circumstances)

Most chronic pain states are not relieved by opioid drugs:

central pain
trigeminal neuralgia (tic douloureux)
causalgia
phantom limb pain
cancer pain
lower back pain

These pain states require continuous medication
Therapy limited by tolerance and physical dependence

Chronic pain arising from **terminal illness** can be relieved by opioid drugs

ii. Acute Pain

postoperative pain
diagnostic procedures
orthopedic manipulations
myocardial infarction

iii. Preanesthetic medication (fentanyl-derivatives)

iv. Dyspnea

v. Cough Suppression (codeine, dextromethorphan)

vi. Diarrhea and dysentery

CONTRAINDICATIONS

i. Decreased respiratory reserve

emphysema
severe obesity
asthma

ii. Biliary colic

iii. Head injury

iv. Reduced blood volume

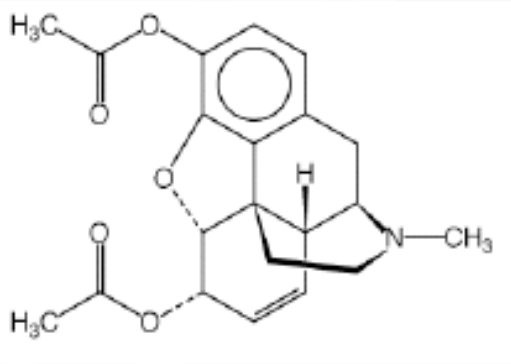
v. Hepatic insufficiency

vi. Convulsant states

Opioid Analgesics

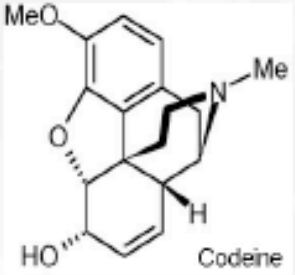
Heroin (diamorphine):

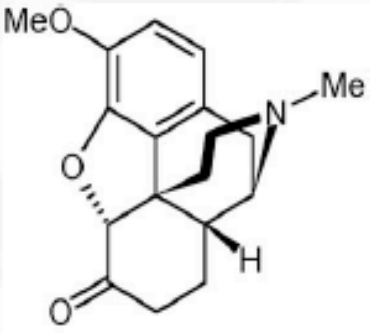
- Diacetylated morphine
- Greater lipophilicity => crosses blood/brain barrier better => greater "rush"
- Used in UK as analgesic (~2x more potent than morphine)



Hydrocodone (Vicodin®):

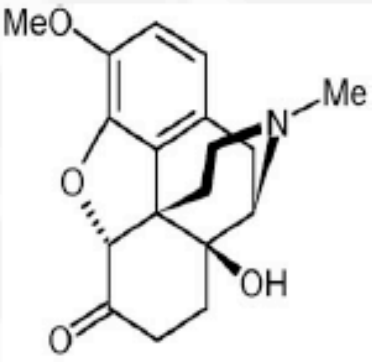
- Often combined with NSAIDs
- Contained in over 200 preparations in the US





Oxycodone (OxyContin®):

- Used in slow-release formulation to treat chronic pain
- People seeking an alternative to heroin often try OxyContin. They chew the time-release tablets for a quicker high. Some crush the tablet to snort or inject it. Prescriptions are often obtained fraudulently, and in many robberies of pharmacies, only Oxycontin is stolen.



Opioid Analgesics

Meperidine (Pethidine):

- Actions similar to morphine
- Much shorter duration => used during labour

Methadone:

- Actions similar to morphine
- Significantly longer duration ($t_{1/2}$ = >24 h) => less psychological dependence
- Used to treat morphine and heroin addiction

Etorphine:

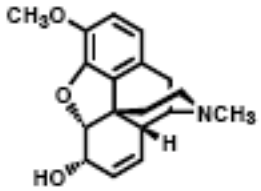
- 1000x more potent than morphine, but similar efficacy
- No clinical advantage
- Used to immobilize wild animals (high potency permits small volumes in darts)

Fentanyl:

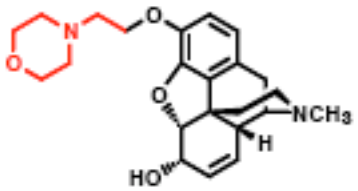
- High potency (allows use in transdermal delivery systems)
- Short lasting: used in anesthesia and in patient-controlled infusion systems

Antitussive activity

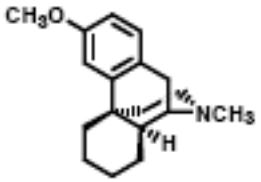
- "non-narcotics" eg. diphenhydramine
- "narcotics"



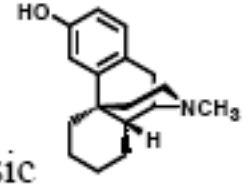
codeine
10-20 mg



pholcodine
5-10 mg

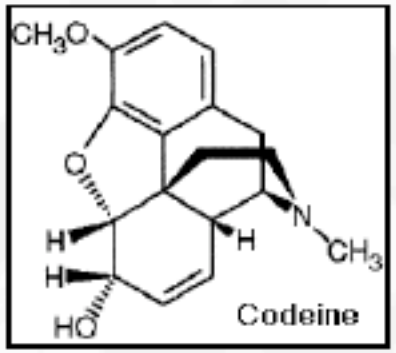


dextromethorphan (+)
10-20 mg



Note levorphanol = (–)-isomer = analgesic

Opioid Analgesics

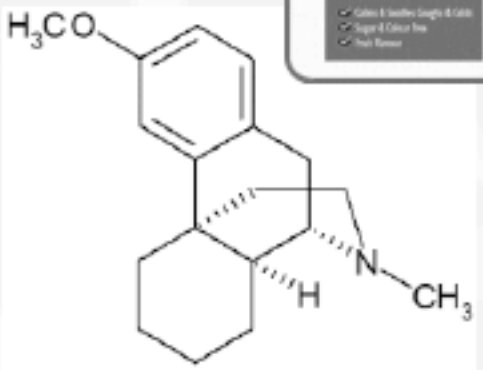


Codeine (3-methoxy-morphine):

- Better oral absorption than morphine
- Only 20% of analgesic effect of morphine
  (does not increase significanly by increasing the dose)
- Prodrug: Converted into morphine by demethylation via CYP2D6
  (mutated in ~10% of the population => resistance to the analgesic effect)
- CYP2D6 inhibitors (e.g. Fluoxetine) reduce efficacy of Codeine
- Little euphoria => rarely addictive
- GI and respiratory effects similar to morphine
  (=> codeine and dihydrocodeine are widely used as antitussiva)

Dextromethorphane (DXM):

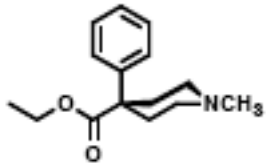
- Synthetic morphine derivative
- Equally antitussive as codeine
- Does not act through opioid receptors
- No analgesic or GI effects



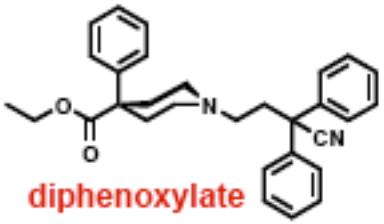
Antidiarrhoeals related to pethidine

Diphenoxylate and Loperamide

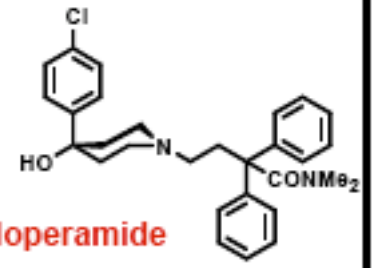
- Developed from pethidine
- Selective antidiarrhoeal activity
- Orally active - main activity in GIT
- ↓ peristalsis etc
  - selective distribution?
- subtherapeutic dose of atropine in diphenoxylate



pethidine

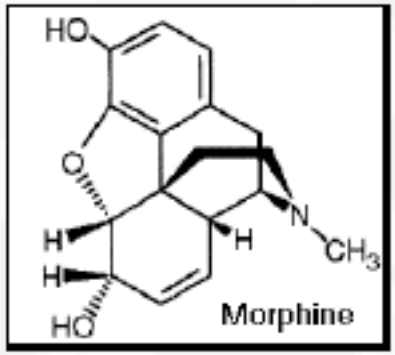


diphenoxylate



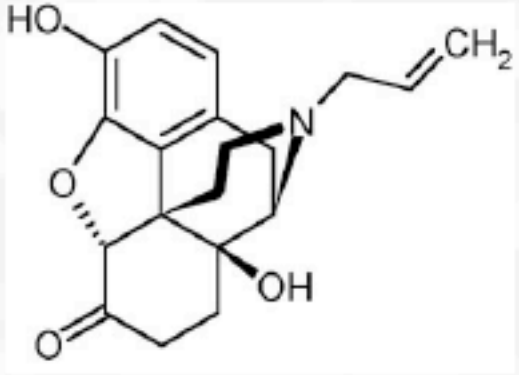
loperamide

Opioid Analgesics

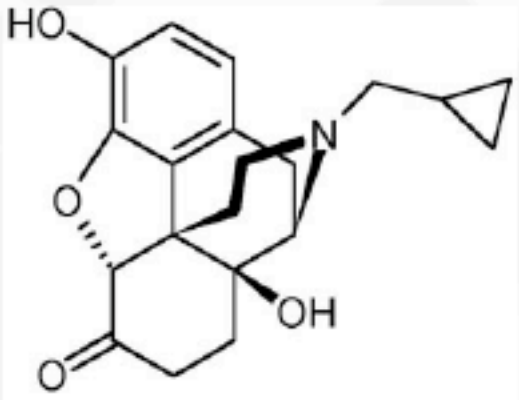


Opiate antagonists:

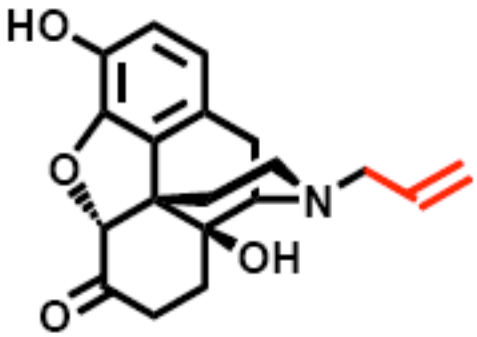
- Naloxone:
  - Short acting
  - Rapidly reversed opoid-induced analgesia and respiratory suppression
  - No effect if no opioids are present
  - Used to treat opiate overdoses and to improve breathing in newborns whose mothers received opioids
  - Induces severe withdrawal symptoms in opioid addicts



- Naltrexone:
  - Similar to naloxone, but much longer duration of action
  - Used to "protect" detoxified addicts by preventing any opioid effect if the patient relapses



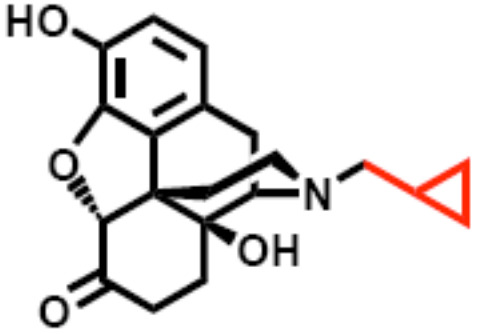
Opioid antagonists



naloxone

- derivative of oxymorphone
- $NCH_3 \rightarrow$ N-allyl
- pure antagonist at μ opioid receptors
- half-life less than heroin/morphine
- used to prevent death from heroin overdose
- 100 – 1000 times less active orally than parenterally

naltrexone



- $NCH_3 \rightarrow$
- orally active about 8 x naloxone
- as treatment for opioid addiction?
- other activity – decreases craving
  - represses urge for alcohol

Buprenorphine Pharmacology

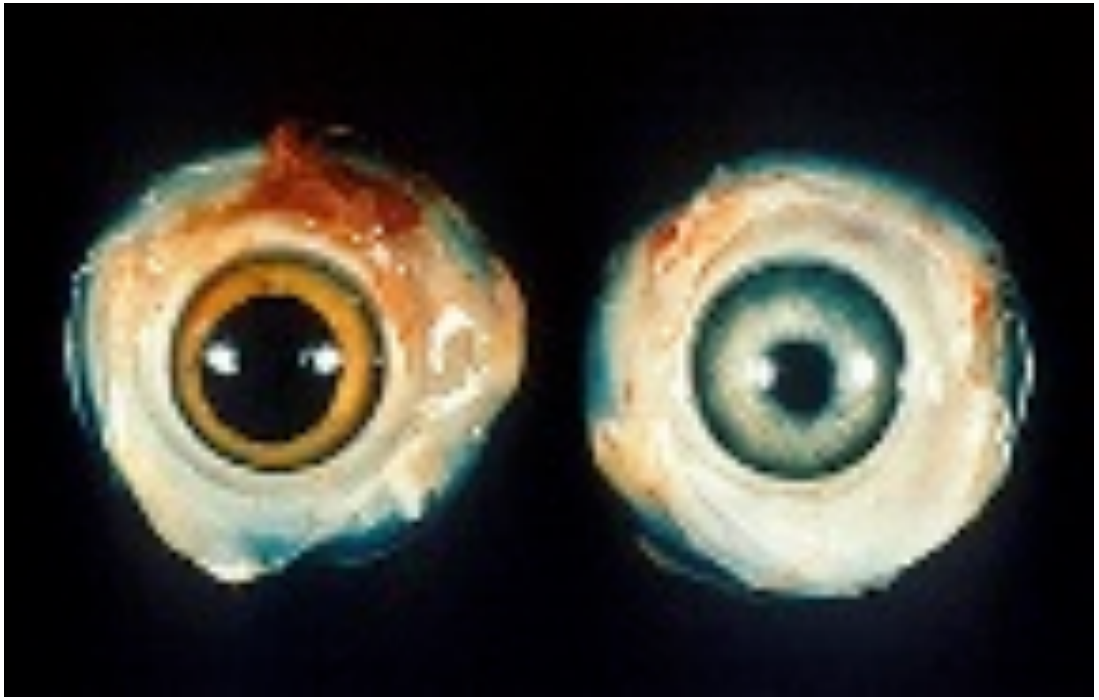
- Partial agonist at mu receptor
- High affinity for mu receptor
- Can displace full opiate agonist such as heroin or methadone
  - Displacement of heroin or methadone by buprenorphine can produce opiate withdrawal symptoms

Buprenorphine Pharmacology

- Antagonist at kappa receptor
- Poor bio-availability taken orally (extensive first pass metabolism)
- Much more bio-available from sublingual mucosa (Peak 2-3 hours following sublingual dose)

OPIATE INTOXICATION, OVERDOSE AND WITHDRAWAL

INTOXICATION OR WITHDRAWAL?



Withdrawal

Intoxication

OPIATE OVERDOSE

- CLASSIC TRIAD SEEN IN OVERDOSE
  - Miosis
  - Coma
  - Respiratory depression

OPIATE OVERDOSE TREATMENT

- NARCAN (NALOXONE)
  - 0.4 mg IV push, if no response, then 2 mg IV push every 2 - 3 minutes until a total dose of 10 mg is given or a response.

  - Half-life of naloxone is shorter than that of morphine

Addiction and Dependence

- **<u>Drug addiction</u> is a condition in which an individual has lost the power of self-control with reference to a drug and abuses the drug to such an extent that the individual, society, or both are harmed.**
- **<u>Dependence</u> refers to a state resulting from habitual use of a drug, where negative physical withdrawal symptoms result from abrupt discontinuation.**
- **The key is that addiction results when the reward pathways in the brain are stimulated by drug use thereby causing dependence due at least in part to psychological reasons.**
- **Dependence implies need of the drug to avoid withdrawal symptoms, not to gain a reward response in all cases. Palliative care patients do not experience a "high" when taking an opioid and are therefore not considered to be addicted.**

OPIATE WITHDRAWAL

- In general, opiate withdrawal signs and symptoms are the same for all opiates; what differs is the time of onset and the length and intensity of withdrawal.
- The withdrawal is divided into early, middle and late phases to show the progression of symptoms when the patient is not treated.

OPIATE WITHDRAWAL - EARLY

- Lacrimation (eyes water)
- Yawning
- Rhino rhea (runny nose)
- Sweating

SENSE OF ANXIETY AND DOOM, THOUGH NOT LIFE THREATENING

OPIATE WITHDRAWAL - MIDDLE PHASE

- Restless sleep
- Dilated pupils (mydriasis)
- Anorexia
- Gooseflesh
- Irritability
- Tremor

OPIATE WITHDRAWAL - LATE PHASE

- Increase in all previous signs and symptoms
- Increase in heart rate
- Increase in blood pressure
- Nausea and vomiting
- Diarrhea
- Abdominal cramps
- Labile mood
- Depression
- Muscle spasm
- Weakness
- Bone pain

HEROIN WITHDRAWAL TIME FRAME

- 1/2 life is 2 - 3 hours
- Onset after last dose is 8 - 12 hours
- Peak is 48 hours
- Duration is 5 - 10 days

*Longer-acting opiates have more prolonged ½ lives and the onset of withdrawal is delayed as compared to heroin.

PROTRACTED OPIATE WITHDRAWAL

- CAN LAST UP TO 9 MONTHS WITH SOME OR ALL OF THE FOLLOWING:
  - Weight gain
  - Increased basal metabolic rate
  - Decreased temperature
  - Increased respiratory rate
  - Increased blood pressure
  - Menstrual irregularities (secondary to increased prolactin hormone levels)

OPIATE WITHDRAWAL TREATMENT

- CAN BE INPATIENT OR AMBULATORY DETOX
  - Involves the use of medication to damper the increased signs of opiate withdrawal
    - Buprenorphine has recently been approved for use by authorized physicians
    - Methadone can be used if a detoxification program has the proper approvals

Addiction and Dependence

- **<u>Drug addiction</u> is a condition in which an individual has lost the power of self-control with reference to a drug and abuses the drug to such an extent that the individual, society, or both are harmed.**
- **<u>Dependence</u> refers to a state resulting from habitual use of a drug, where negative physical withdrawal symptoms result from abrupt discontinuation.**
- **The key is that addiction results when the reward pathways in the brain are stimulated by drug use thereby causing dependence due at least in part to psychological reasons.**
- **Dependence implies need of the drug to avoid withdrawal symptoms, not to gain a reward response in all cases. Palliative care patients do not experience a "high" when taking an opioid and are therefore not considered to be addicted.**

TOLERANCE

Tolerance develops to:

- **Analgesia**
- **Euphoria**
- **Sedation**
- **Lethal dose**
- **Nausea**

Tolerance DOES NOT develop to:

- **Miosis**
- **Constipation**
- **Cross –tolerance develops to other opioids**

Opioid Addiction and Treatments- Overview

- What are Opioids?
- Addiction and Dependence
- Mechanism of Dependence
- Tolerance
- Treating Addiction
  - Cold Turkey Approach
  - Traditional Drug Treatment
  - Rapid Detoxification
- Conclusions and Future Avenues For Research

Mechanism of Dependence and Addiction

- Dependence occurs when, after a constant supply of the opiate, the brain shows adaptation, or changes in its circuitry. When that drug is taken away, neurons that have been inhibited start pumping out neurotransmitters again. This imbalance of chemicals in the brain interacts with the nervous system to produce the classic opiate withdrawal symptoms: nausea, muscle spasms, cramps, anxiety, fever, diarrhea.

Tolerance

- **Tolerance, describes the need for a drug user to administer larger and larger doses of the drug to achieve the same psychoactive effect.**
- **When the body's chemical equilibrium is upset, as in habitual drug-taking, the body sets up oppositional processes to restore itself. More of the drug is needed to overcome these efficient corrective processes.**
- **While considerable debate exists about the mechanisms of opioid tolerance, two factors have been isolated with a degree of certainty.**
  1. **Receptor Downregulation- Opioid receptors in the body are actively reduced due to overexposure to opioids. This can also have an effect on endogenous opioid peptide function (i.e. regular functioning of endorphins)**
  2. **Antiopiates- Chemicals like neuropeptide FF, orphanin FQ/nociceptin, and Tyr-W-MIF-1 have all been found to block the function of opioids. This activity is due to the fact that these drugs can block g-protein activity.**

cAMP involvement in morphine's tollerance and withdrawal

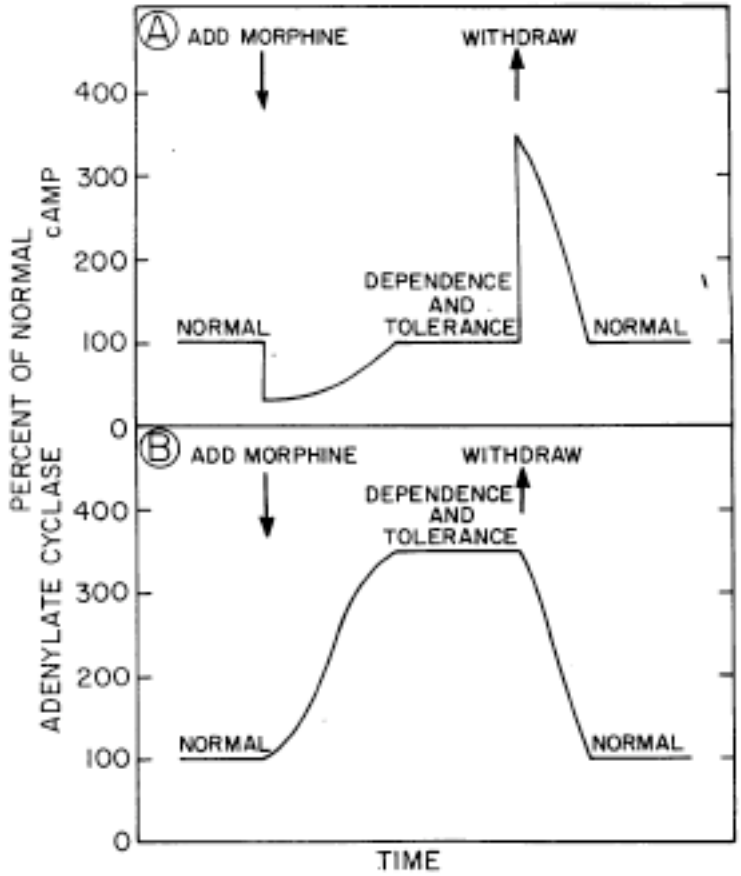


FIG. 1. A model of the role of adenylate cyclase regulation in the development of morphine tolerance and dependence. Part A shows the effects of morphine upon cAMP levels, and part B, the effects of the opiate upon adenylate cyclase activity as a function of time.

Proc. Nat. Acad. Sci. USA
Vol. 72, No. 8, pp. 3092–3096, August 1975
Biochemistry

Treatments

- Several treatments and treatment strategies exist for opioid addiction.
  1. The Cold Turkey Approach
  2. Traditional Opioid Drug Treatment
  3. Rapid Detoxification

The Cold Turkey Method

- Quitting opioid use cold turkey after dependence has developed has several drawbacks but also some advantages.
- Of course, this is the cheapest method of ending dependence. This body, however, is put through a significant amount of stress during the “withdrawal” period.
- Death or seizures almost never result from opioid withdrawal unless the amount of opioid being withdrawn was extremely large. These events are more likely to occur during withdrawal from barbiturates or benzodiazepines.

The Cold Turkey Method- Withdraw

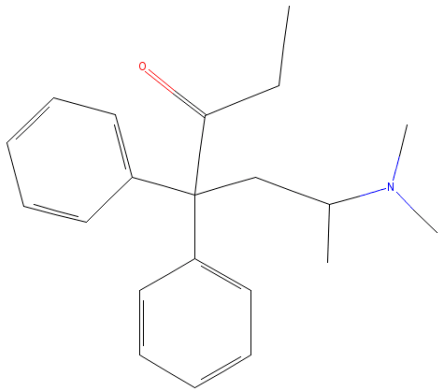
- About eight to twelve hours after the last heroin use, an addict's eyes begin to tear and he/she starts to experience flu-like symptoms: sneezing, weakness, depression, muscle cramps, nausea, vomiting, diarrhea. The symptoms increase in severity over two to three days.
- Within a week to 10 days the illness is over.
- The phrase 'cold turkey' probably comes from the appearance of goose bumps all over the body, which resembles a plucked turkey. Muscle spasms in the legs produce kicking movements, and this may be the derivation of the expression 'kick the habit.'

Traditional Drug Based Treatments

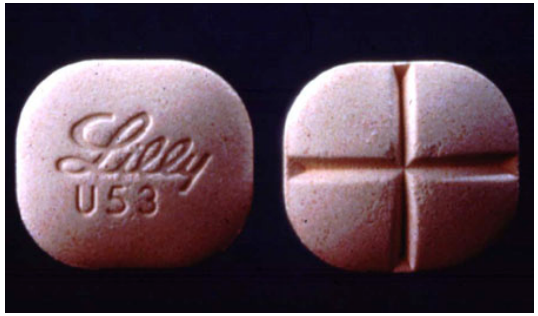
- The primary method of treating and managing opioid addiction and dependence has been with the use of other opioid drugs.
- These replacement drugs function to essentially wean the user off of opioid use.
- Most of these drugs have withdrawal symptoms lighter than those of the abused opioid (heroin, Oxycontin, morphine, etc…)

Traditional Drug Based Treatments- Methadone

- **A synthetic opioid, used medically as an analgesic and in the treatment of narcotic addiction.**
- **Although chemically unlike morphine or heroin, methadone also acts on the opioid receptors and thus produces many of the same effects. Chemically, methadone is the simplest of the opioids.**
- **Methadone has a slow metabolism and very high lipid solubility, making it longer lasting than morphine-based drugs. Methadone has a typical half-life of 15 to 60 hours, in rare cases up to 190 hours. permitting the administration only once a day in heroin detoxification and maintenance programs.**
- **Methadone has traditionally been provided to the addiction population in a highly regulated methadone clinic, generally associated with an outpatient department of a hospital.**
- **Numerous clinics start addicts at 30mg and raise the dosage 10mg a day until the addict feels they are at a comfortable level of dosage.**



Traditional Drug Based Treatments- Methadone, continued…

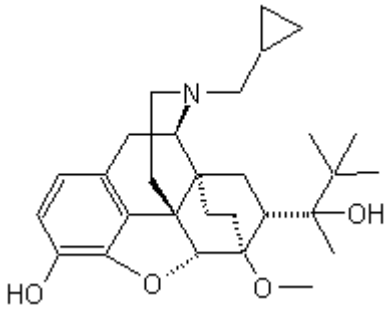


- At proper dosing, methadone usually reduces the appetite for and need to take heroin.
- However, most heroin addicts report more difficulty in quitting methadone than heroin.
- While there is much debate over the treatment schedule and duration required, treatment at a methadone maintenance clinic is intended to be for an indefinite duration.
- Many factors determine the treatment dose schedule, and some follow the philosophy that methadone maintenance treatment is not curative for heroin addiction.

Traditional Drug Based Treatments- Methadone- History

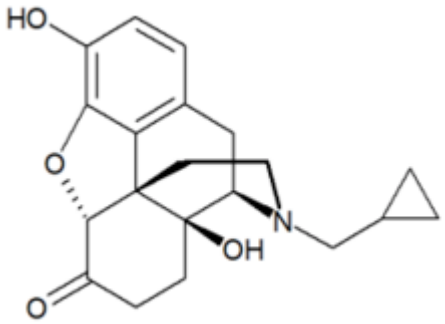
- Methadone/dolophine, was first synthesized in 1937 by German scientists Max Bockmühl and Gustav Ehrhart at IG Farben during their search for an analgesic that would be easier to use during surgery (and less potentially addictive, post-op) than morphine…)
- Methadone was introduced into the United States in 1947 by Eli Lilly and Company as an analgesic.
- A great deal of anecdotal evidence was available "on the street" that methadone might prove effective in treating heroin withdrawal and it had even been used in some hospitals. It was not until studies performed at the Rockefeller University in New York City by Professor Vincent Dole, along with Marie Nyswander and Mary Jeanne Kreek, that methadone was systematically studied as a potential substitution therapy.
- To date, methadone maintenance therapy has been the most systematically studied and most successful, and most politically polarizing, of any pharmacotherapy for the treatment of drug addiction patients.

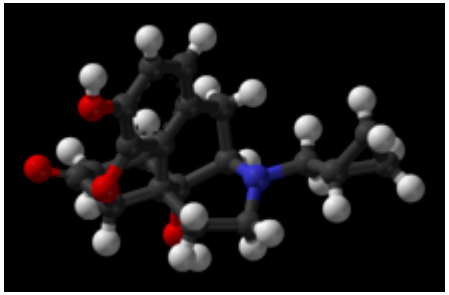
Traditional Drug Based Treatments- Buprenc



- an opioid drug with partial agonist and antagonist actions.
- In October 2002, the FDA additionally approved Suboxone and Subutex, buprenorphine's high-dose sublingual pill preparations for opioid addiction.
- Belongs in the Schedule III category of drugs along with hydrocodone and anabolic steroids.
- Advantages to using buprenorphine over methadone include less restrictive availability. A patient can be prescribed the drug for self administration rather than having to receive their dose at a clinic.
- Also, it is thought that Buprenorphine has less severe withdrawal symptoms than methadone although the symptoms may last longer.

Traditional Drug Based Treatments- Naltrexone





- Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence.
- Naltrexone, and its active metabolite 6-β-naltrexol, are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors. The plasma half-life of Naltrexone is about 4 h, for 6-β-naltrexol 13 h. The blockade of opioid receptors is the basis behind its action in the management of opioid dependence—it reversibly blocks or attenuates the effects of opioids.
- Because the drug is merely a receptor antagonist, it blocks the effects of opioids but does not reduce the craving for opioids.
- As such, Naltrexone is found to be effective mostly for treatment of people in stable social situations such as addicted health care professionals.
- Even so, compliance with treatments is a continuing problem for which implantable Naltrexone release devices are being increasingly used.

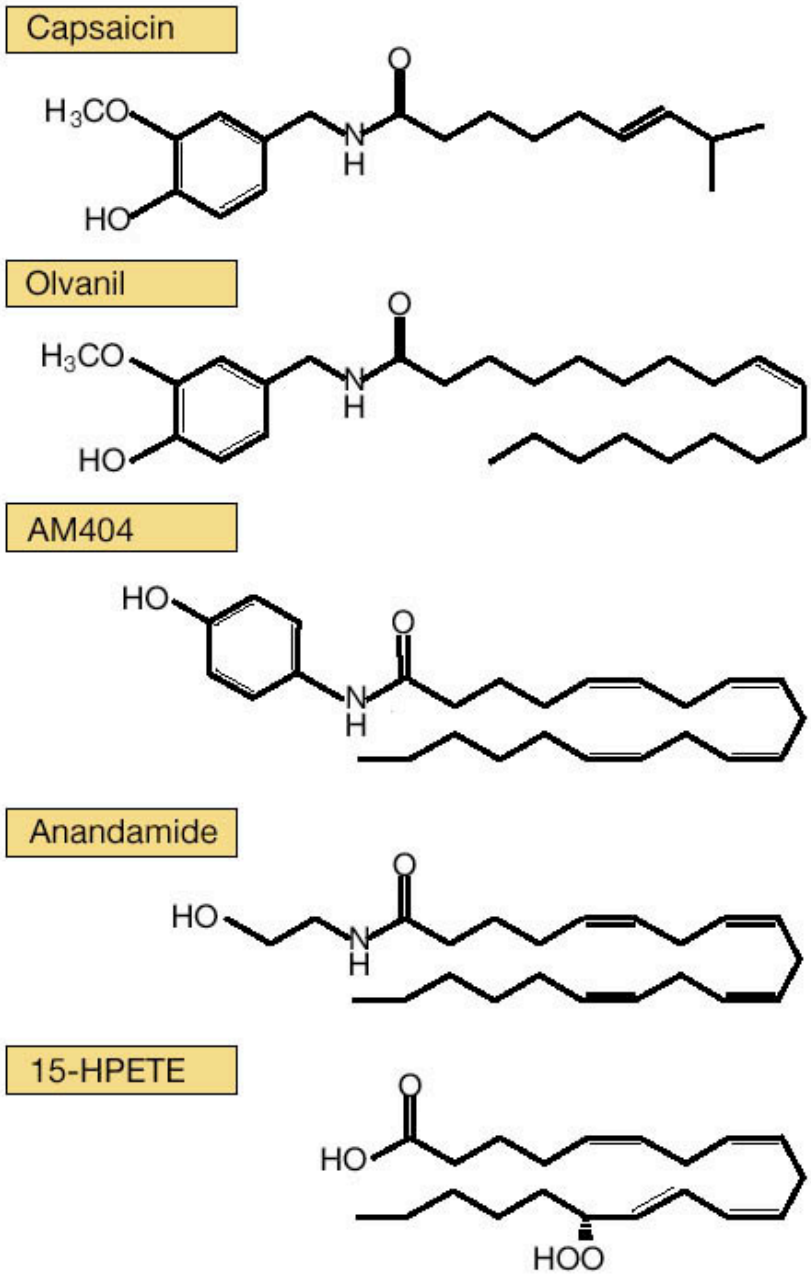
Rapid Detoxification

- A technique that aims to reduce the duration and intensity of opioid withdrawal by administering a combination of drugs while the patient is under general anesthesia.
- The process involves intubation and external ventilation of the patient coupled with the administration of opioid receptor antagonists (blockers).
- The most often used drugs are Naloxone and Naltrexone.
- Naloxone is a powerful Mu opioid receptor antagonist that is capable of rapidly displacing other opioids from the opioid receptors.
- As a result, massive withdrawal symptoms are triggered but are attenuated by the fact that the patient is under anesthesia.
- As with Naltrexone treatment alone, the Rapid Detoxification procedure cannot reduce the craving aspect of addiction and traditional drug based follow up treatments are necessary to manage the addiction although dependence has ended.

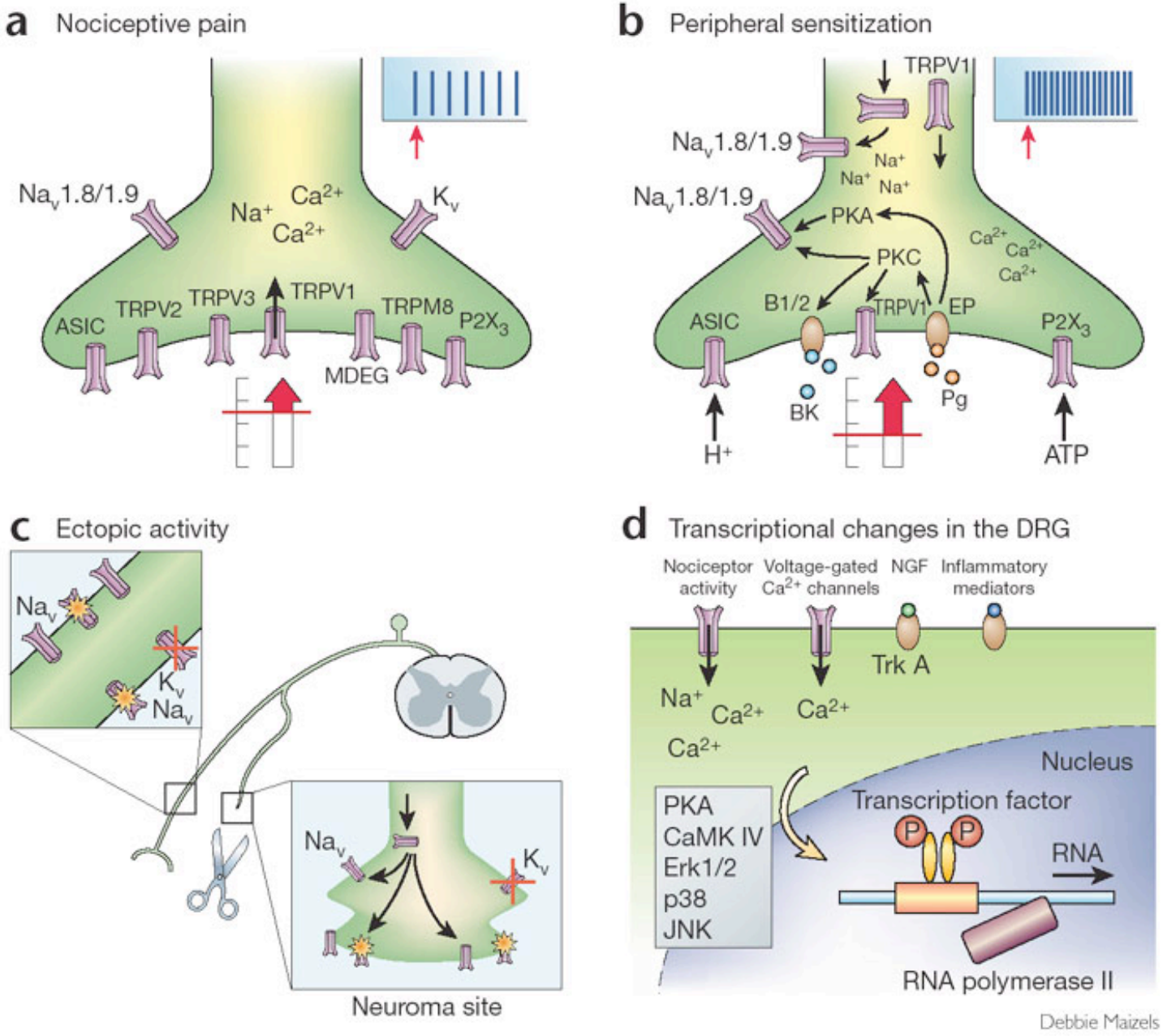
Patient undergoing Rapid Detox

Conclusions

- Opioid addictions is a serious issue that must be given me's ore thought than at present in the scientific community as well as in politics.
- Current treatments are only partially successful in breaking the hold of addiction and dependence on the addict.
- Research can and must be done into other treatments and drugs that are more effective in not only reducing physical dependence and withdrawal symptoms but also in blocking addict's tendency to continue to crave the drug.



Olvanil is a synthetic, non-pungent capsaicin analogue that activates VR1 with relatively slow kinetics. Anandamide is an endogenous lipid metabolite (similar in structure to arachidonic acid) that was initially discovered as a ligand for cannabinoid receptors. AM404 is a synthetic drug that blocks cellular re-uptake of anandamide. Both compounds activate native and cloned vanilloid receptors *in vitro* with relatively slow kinetics, similar to olvanil. 15-HPETE and other lipoxygenase products of arachidonic acid metabolism activate VR1 *in vitro* with potencies (1–10 M) resembling those of anandamide and AM404.



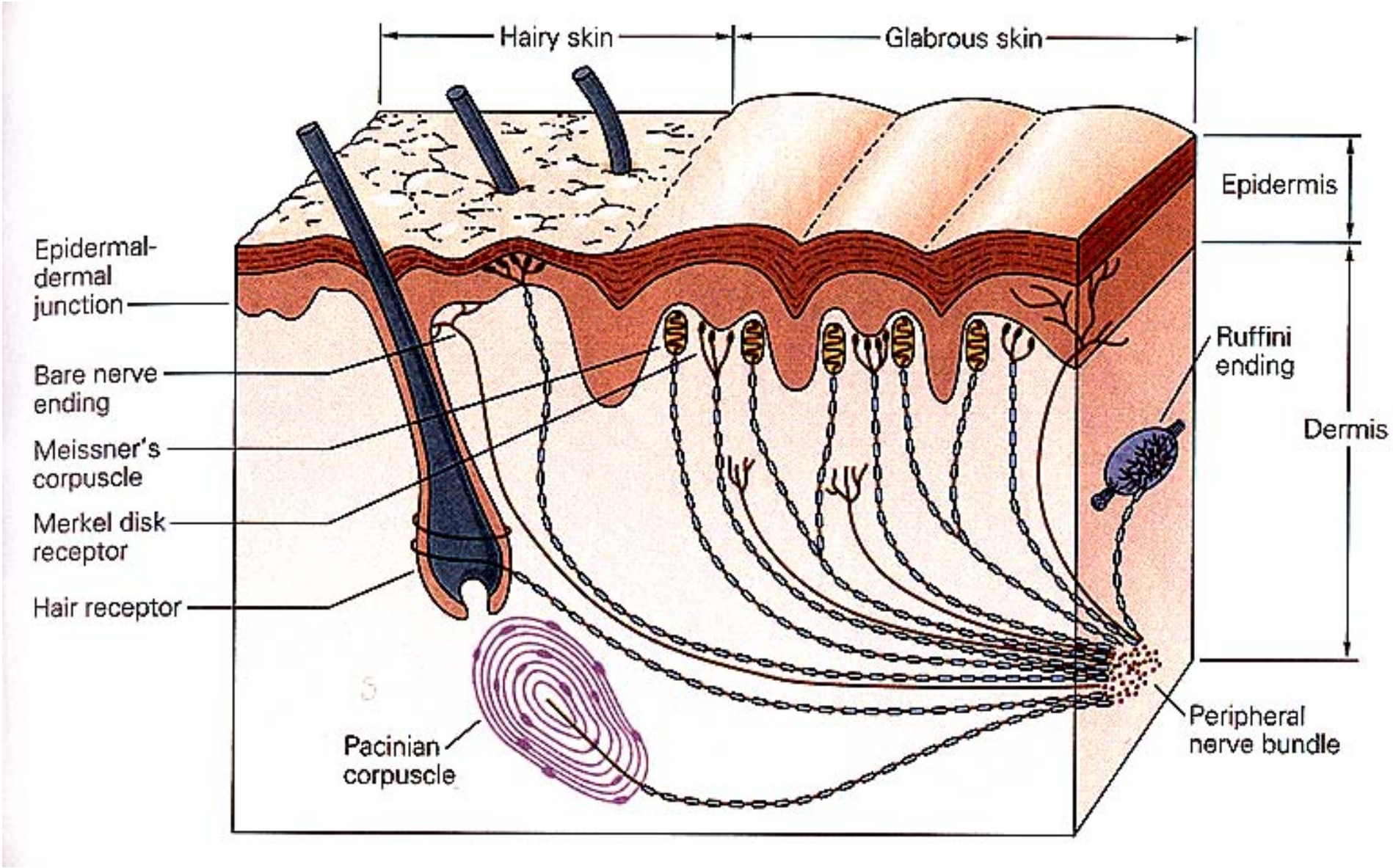
Nociceptor-mediated pain is driven by activation of peripheral nociceptor sensory fibers.

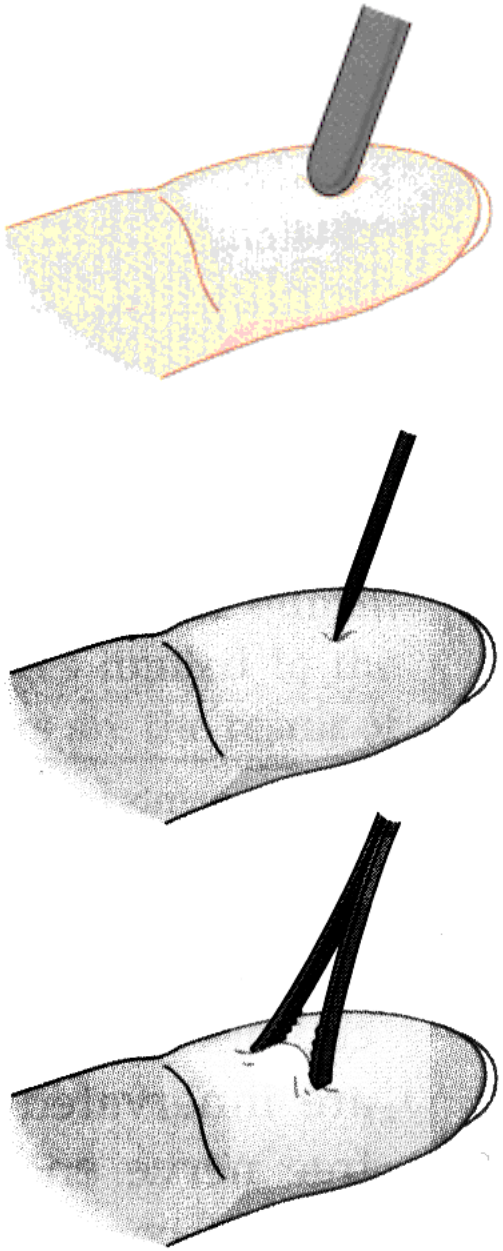
(a) Nociceptive pain is produced by noxious stimuli acting on high-threshold nociceptors.

(b) of the 'inflammatory soup', such as bradykinin or PGs, bind to G-protein-coupled receptors and induce activation of PKA and PKC in nociceptor peripheral terminals, which then phosphorylate ion channels and receptors. As a result, the threshold of activation of transducer receptors such as TRPV1 is reduced, and the excitability of the peripheral terminal membrane increases, producing a state of heightened sensitivity, termed 'peripheral sensitization'.

(c) After injury to nociceptor neurons, increases in transcription or altered trafficking of sodium channels as well as a reduction in potassium channels increases membrane excitability sufficiently so that action potentials are generated spontaneously (ectopic activity).

(d) Activity-dependent signal transduction cascades and signaling pathways downstream to receptors bound by cytokines and growth factors act to modify transcription in nociceptor neurons. Altered production of numerous proteins modifies the phenotype of the neurons, changing their transduction, conduction and transmission properties.


Hairy skin
Glabrous skin
Epidermis
Dermis
Epidermal-dermal junction
Bare nerve ending
Meissner's corpuscle
Merkel disk receptor
Hair receptor
Ruffini ending
Pacinian corpuscle
Peripheral nerve bundle



A Probe with blunt object

Afferent fiber recording

100
50
30

Force (grams)

B Pinprick

100
50
30

C Pinch with serrated forceps

Squeeze

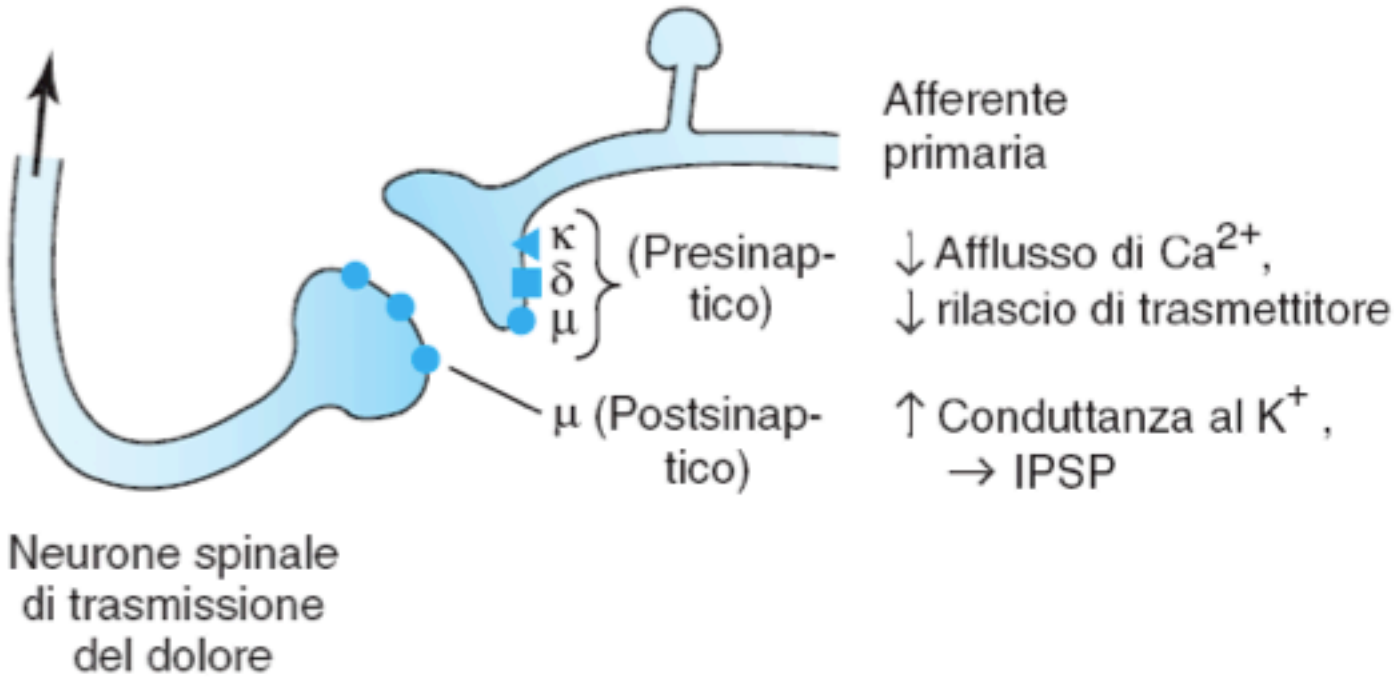
1 s

Source of opiates

- Opium poppy grown in Tasmania, Turkey, etc.
- Opium is the air-dried milky exudate

→ mix of about 20 alkaloids

Figura 31-2. Siti spinali dell'azione degli oppioidi. Gli agonisti mu (μ), delta (δ) e kappa (κ) riducono il rilascio di trasmettitori dai terminali presinaptici delle afferenze nocicettive primarie. Gli agonisti μ iperpolarizzano anche i neuroni della trasmissione del dolore di secondo ordine aumentando la conduttanza del K^+, evocando un potenziale inibitorio postsinaptico.



CANALI IONICI E NUOVI FARMACI ANALGESICI

Anche il dolore acuto più intenso (che dura ore o giorni) può normalmente essere ben controllato – con azioni sfavorevoli significative, ma tollerabili – con gli analgesici attualmente disponibili, specialmente gli oppioidi. Il dolore cronico (che dura da settimane a mesi), tuttavia, non viene controllato in maniera soddisfacente con tali farmaci. È noto oggi che, nel dolore cronico, i recettori presinaptici localizzati sulle terminazioni nervose sensitive periferiche contribuiscono alla aumentata eccitabilità di queste ultime (sensibilizzazione periferica). Il neurone ipereccitabile "bombarda" il midollo spinale, causando una aumentata eccitabilità delle corna dorsali (sensibilizzazione centrale). Questi cambiamenti sembrano essere importanti negli stati infiammatori cronici e nel dolore neuropatico (Basbaum, 1999; Woolf, 2000).

Nel tentativo di scoprire farmaci analgesici più efficaci nel controllo del dolore cronico, si sta rinnovando l'attenzione alla trasmissione sinaptica dello stimolo nocicettivo ed all'elaborazione sensitiva. Canali ionici ligando-dipendenti potenzialmente importanti associati con questi processi in periferia includono la famiglia di recettori a potenziale transitorio o TRPV1 (recettore per la capsaicina), che è attivata dalla sensazione di caldo e da mediatori dell'infiammazione, e i recettori P2X (che rispondono alle purine rilasciate nei tessuti). Uno speciale canale per il sodio resistente alla tetrodotossina e voltaggio dipendente (Nav 1.8), il cosiddetto canale PN3/SNS, è apparentemente associato unicamente con i neuroni nocicettivi nei gangli delle radici dorsali. La mexiletina, che è utile in alcuni stati di dolore cronico, può agire bloccando questo canale. Alcuni bloccanti dei canali voltaggio-dipendenti di tipo N per il calcio hanno mostrato effetti analgesici. Un peptide sintetico correlato alla tossina del serpente marino, la ω-conotossina, che blocca selettivamente questi canali per il calcio, è attualmente in corso di sperimentazione clinica come analgesico. La gabapentina, un anticonvulsivante analogo del GABA (si veda il cap. 24), rappresenta un efficace trattamento per il dolore neuropatico (da lesione del nervo). Recentemente si è dimostrato che essa blocca il dolore e l'iperalgesia associata con l'infiammazione. Siti potenziali di azione della gabapentina includono la famiglia di canali del calcio α-2-δ.

I recettori NMDA sembrano svolgere un ruolo molto importante nella sensibilità centrale a livello sia spinale che sopraspinale. Sebbene alcuni antagonisti NMDA abbiano attività analgesica in modelli animali (ad es. la ketamina), è stato difficoltoso trovare un agente attivo con una tossicità accettabilmente bassa. Il GABA e l'acetilcolina (quest'ultima attraverso i suoi recettori nicotinici) sembrano controllare il rilascio sinaptico centrale di molti neurotrasmettitori coinvolti nella nocicezione. La stessa nicotina e alcuni suoi analoghi possono causare analgesia. Un agonista nicotinico trovato in alcune rane (epibatidina) ha un significativo effetto analgesico.

Sebbene nessuno degli studi descritti abbia finora portato ad un farmaco analgesico approvato per l'uso clinico, essi hanno già fornito una migliore comprensione della nocicezione e della analgesia.

Dal Volume: Farmacologia generale e clinica

Piccin Nuova Libraria S.p.A.

Tabella 31-3. Grado di abitudine ad alcuni effetti degli oppioidi

Elevato grado di abitudine	Moderato grado di abitudine	Minimo grado o assenza di abitudine
Analgesia Euforia, disforia Obnubilamento Sedazione Depressione respiratoria Effetto antidiuretico Nausea e vomito Effetto antitosse	Bradicardia	Miosi Stipsi Convulsioni

Tabella 31-4. Effetti sfavorevoli degli analgesici oppioidi

Irrequietezza, tremore, iperattività (nelle reazioni disforiche)
Depressione respiratoria
Nausea e vomito
Aumento della pressione endocranica
Ipotensione posturale accentuata dall'ipovolemia
Stipsi
Ritenzione urinaria
Prurito intorno al naso, orticaria (più frequente in seguito a somministrazione parenterale)

Tabella 31-5. Interazioni tra analgesici oppioidi ed altri farmaci

Gruppo farmacologico	Interazioni con gli oppioidi
Sedativoipnotici	Potenziamento della depressione del sistema nervoso centrale e, in particolare, della depressione respiratoria.
Tranquillanti antipsicotici	Aumentata sedazione. Effetti variabili sulla depressione respiratoria. Potenziamento degli effetti cardiovascolari (azioni antimuscariniche ed α-bloccanti).
MAO-inibitori	Controindicazione relativa all'uso di tutti gli analgesici stupefacenti per l'elevata incidenza di coma iperpiretico; sono stati descritti anche casi di ipertensione.